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Adrenal tumor of the ovary with masculinization

A case report

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OVARIAN tumors having a cell structure resembling the adrenal cortex have been referred to as adrenal rest tumors, masculinovoblastoma, luteoma, luteinoma, and virilizing lipoid cell tumors of the ovary.[1] This varied terminology is brought about by the uncertainty of origin. Such tumors are quite rare, Lees and Paine[2] giving the number reported as 35 by 1958.

The following case occurred in a young woman, previously normal, who developed symptoms of defeminization and masculinization over a period of several years.

J. R., a 26-year-old Negro graduate nurse was seen in December, 1955, giving a history of amenorrhea for 1 year. During the preceding 6 years her periods had become further apart, varying from 6 weeks to 3 months, until there was total amenorrhea by 1955. Occasional periods would last 10 or 12 days, with a scanty flow. Beginning about August, 1954, she noted a growth of facial hair which increased until shaving three times a week was necessary. Hair growth had increased over the lower abdomen. She had not noted any breast changes or voice changes. Menarche had been at the age of 11½ years. Periods were normal until the age of 19 years (1948) when the episodes of amenorrhea began. She had been married 3 years, used no contraception, and had not become pregnant.

Examination revealed a normal body configuration with a growth of hair on the face and chin and male distribution of pubic hair. The breasts were normal. The clitoris was 2 cm. long and 1 cm. in diameter. The cervix was extremely soft and deep bluish red in color. The uterus was soft and symmetrically enlarged to 5 or 6 cm. above the symphysis (about the size of a 2½ months' pregnancy). The right ovary was enlarged to 5 or 6 cm. in diamter. The blood pressure was 140/80, but over the next

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few months varied between 130/80 and 190/110, remaining mostly in a medium range.

Laboratory data. Red blood count was 4.89 million per cubic millimeter; hemoglobin level, 15.2 Gm.; white blood count, 10,300 per cubic millimeter; blood cholesterol level, 223 mg. per 100 c.c. The glucose tolerance curve was normal. Urinary 17-ketosteroid level was 44 mg. per 24 hours. (Zimmermann method; normal 5 to 15 mg. per 24 hours.) X-ray examination showed the sella turcica to be normal. An intravenous pyelogram revealed a round mass in the center of the pelvis, interpreted to be the uterus. A pregnancy test was negative on two occasions. Endometrial biopsy twice showed atrophic endometrium. A month later the 17-ketosteroid level was 94 mg. per 24 hours. A cortisone suppression test was done (12.5 mg. of cortisone acetate every 6 hours for 12 days), after which the 17-ketosteroid level was 89.6 mg. per 24 hours.

At operation on Sept. 7, 1956, the right ovary was removed. The left ovary was normal. The uterus was 8 cm. in diameter at the fundus and was soft, smooth, and deep bluish red in color. Both adrenal areas were negative to palpation. The right ovary was 6 cm. in diameter, moderately firm, with a smooth whitish capsule. The cut surface revealed soft dark brown tissue covered by a thin white cortex. There were a few scattered yellowish areas. Microscopic examination (Fig. 1) revealed large polyhedral cells with abundant cytoplasm and ovoid, vesicular nuclei, the general appearance being identical with that of an adrenal cortical adenoma (pathologist's report). The brownish color was due to hemorrhage into the tumor. The pathologic diagnosis was adrenal cortical tumor of the ovary, corroborated by Dr. Emil Novak,[3] who examined some of the sections.

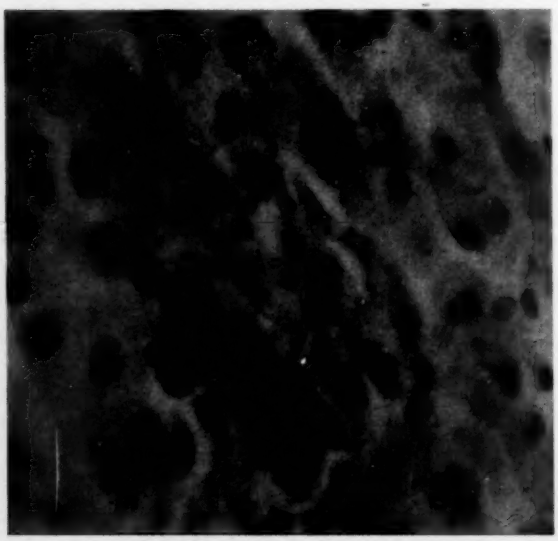

Fig. 1. Adrenal tumor of the ovary. High-power view showing large polyhedral cells with abundant cytoplasm and ovoid, vesicular nuclei. (×450; reduced ⅓.)

On the eighth postoperative day the 17-ketosteroid level was 2.3 mg. per 24 hours. The patient was discharged on the tenth postoperative day in good condition.

Follow-up. Normal periods began 2 months after operation. The facial hair gradually diminished during the following year. The clitoris regressed but remained slightly larger than normal. The uterus reverted to almost normal size. The cervix became normal. One and one-half years after operation the patient became pregnant but miscarried at 22 weeks (16 ounces). A few months later she became pregnant again and went to 34 weeks, giving birth to a 4½ pound female infant who is living and well. At the last examination on Jan. 6, 1961, more than 4 years after operation, there was a small amount of hair on the chin which is shaved about every 3 weeks. The periods are normal and regular, the clitoris was still somewhat larger than normal. The cervix was normal. The uterus was retroverted but otherwise negative. No adnexal masses were palpated. The 17-ketosteroid level was 9.1 mg. per 24 hours on Jan. 16, 1961.

Comment

The symptoms and signs of virilism in this case are similar to those of other reported cases. The changes in the uterus and cervix are unusual. The elevated blood pressure suggests a relation to Cushing's syndrome and the adrenogenital syndrome. In addition to masculinization, with some tumors there is associated glycosuria as well as hypertension, suggesting the production of adrenal hormones other than 17-ketosteroids.[4]

Excessive 17-ketosteriod production is characteristic of adrenal cortical hyperplasia and adrenal cortical tumors, the cortisone suppression test being used to distinguish between them. This is true whether the pathologic process is in the adrenal gland or ovary, and the distinction is important

because hyperplasia responds to cortisone therapy, while surgical intervention is indicated for tumors.

In some adrenal tumors of the ovary the 17-ketosteroid level has not been elevated, yet there is virilism.[2] The explanation may lie in Leventhal's[5] statement concerning the Stein-Leventhal syndrome to the effect that a greater percentage of the component 17-ketosteroids may be androgenic than is normally the case.

Histologically, the cells in this tumor closely resemble adrenal cortical cells. Scully and Morris[1] place these tumors in a heterogeneous group along with those resembling Leydig cells, granulosa lutein, theca lutein, and stromal lutein cells. They observe that 10 of the reported cases resemble Cushing's syndrome, making the origin from adrenal rest cells in the ovary quite likely. They further state that luteinized ovarian stromal cells may produce adrenal cortical hormones, so that the tumor in some cases may be of ovarian cell origin. There is some confusion in differentiating these tumors from luteomas[6] with the probability that where masculinization has been reported with luteoma the tumors were really adrenal in type.

The latter observations are in agreement with Iverson[7] who demonstrated a similarity between adrenal tumors of the ovary and paralutein or theca lutein cells and concluded that all types of functional tumors of the ovary arise from undifferentiated ovarian mesenchyme. It is further noted that while adrenal cell rests are well known to occur in and near the ovary they are more frequent in a later age group and are not associated with virilism.[8]

Regarding a biochemical explanation, progesterone is known to have androgenic capabilities.[7, 9] Also, in cases of adrenogenital syndrome, Jailer[10] postulated that there are enzymatic blocks in the synthesis of hydrocortisone with overproduction of its precursors (17-hydroxyprogesterone and 21-desoxyhydrocortisone) in the adrenal gland. Temporary hypoadrenalism is thus produced and the pituitary secretes more ACTH in an attempt to produce a normal amount of hydrocortisone for homeostasis. This in turn leads to a further piling up of the precursors which escape into the circulation and are metabolized, presumably in the liver, into androgenic substances like androsterone and 11-oxygenated androstane derivatives. These substances are androgenic and cause the characteristic virilism.

Summary

1. A case report of adrenal tumor of the ovary is presented.

2. There was elevation of the 17-ketosteroids, unaffected by cortisone.

3. There were unexplained changes in the uterus and cervix.

4. All symptoms and signs regressed after removal of the tumor.

5. Menses returned to normal and 2 pregnancies occurred within 3 years.

Conclusion

Based on histologic appearance and clinical manifestations this tumor is reported as an adrenal cortical tumor of the ovary.

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The Chiari-Frommel syndrome

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A SYNDROME consisting of amenorrhea, persistent lactation, and uterine-ovarian atrophy in otherwise normal postpartum women was first described by Chiari in 1855.[7] He described 2 such patients and expressed the opinion that the condition was due to the poor nutrition and general health of the patients. Frommel, in 1882, reported a similar case.[16] Since these original descriptions further reports have raised the total of known cases of this syndrome to 18.[1-3, 8, 9, 17, 22, 23, 28] Four patients have been reported to have stopped lactating or to have resumed menstruation.[1, 3, 22, 23] Of these, 2 were reported to have become pregnant again.[3, 23] The shortest duration of the syndrome reported with subsequent resumption of menstruation was 18 months but lactation persisted.[22] The longest duration with recovery was 8 years, with resumption of menstruation and no further lactation.[3] Long-term follow-ups are sparse and no autopsy reports are available.

A case has recently been studied which fits this syndrome, and the patient subsequently became pregnant and was delivered.

Case report

Mrs. J. D., a 31-year-old white woman, was first seen in January, 1959, complaining of amenorrhea and galactorrhea since the birth of her second child 2 years and 4 months before.

She had an abortion at 3 months' gestation in 1953, and was delivered of her first child in March, 1955. She did not breastfeed the infant and her breasts subsided promptly. She was delivered of her second child in September, 1956. She breastfed this infant for 3 weeks, then changed to bottle feeding because of a sore breast. Profuse galactorrhea persisted in spite of attempts to terminate lactation by full estrogen and androgen therapy. Amenorrhea also persisted. There was no headache, visual impairment, or hirsutism. The patient noted periods of marked depression.

Physical examination showed the uterus to be smaller than normal and the breasts to be engorged with milk. Axillary and pubic hair were normal in amount, and pubic hair was feminine in distribution. The external genitals did not show atrophy, and the clitoris was normal in size.

Studies done at the University of Virginia Hospital in February, 1959, were as follows: Visual field determinations were normal. The pituitary sella appeared normal. Results of endocrine studies were considered normal except for a slightly elevated 17-hydroxycorticosteroid excretion of 19.4 and 19.1 mg. per 24 hours. The plasma 17-hydroxycorticosteroid level was 13.8 mg. per 100 c.c. with a rise to 52.3 mg. per 100 c.c. 4 hours later in response to 25 units of ACTH given intravenously. Urinary 17-ketosteroid excretion was 11.7 and 8.6 mg. per 24 hours. Pituitary gonadotropin excretion was positive for 6.6 M.U., negative for 100 M.U. Protein-bound iodine level was 5.4 μg per 100 c.c. Fasting blood sugar level was 92 mg. per 100 c.c.; 2 hours after glucose administration it was 95 mg. per 100 c.c. The hemogram findings were normal except for 9 per cent eosinophils. An endometrial biopsy showed only ciliated columnar epithelium, presumably endocervical in origin. Routine urinalysis, urea, stool, serology, and chest films were normal.

No treatment was instituted at that time. One month later, in March, 1959, she had the first vaginal bleeding since the birth of her child 2½

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years before, and had scant bleeding of 3 or 4 days' duration at monthly intervals until July, 1959. The galactorrhea lessened although milk was still expressible from both nipples. When seen in October, 1959, she was found to be approximately 2 months pregnant. Galactorrhea persisted during the pregnancy though less than just prior to pregnancy. The last 2 weeks of pregnancy were marked by albuminuria and hypertension, and labor was induced. A 4 pound, 3 ounce female infant was delivered under continuous caudal anesthesia in May, 1960. The infant was not breastfed. Stilbestrol was given to the patient for 2 weeks postpartum but galactorrhea persists, more than during the pregnancy but less than at a comparable time following delivery of the second child. She remains amenorrheic to date, now 9 months post partum.

Comment

A consideration of abnormal lactation cannot be pursued with exactness because the mechanism of initiation and maintenance of normal lactation is not completely understood. One of the major difficulties is the absence of accurate and readily reproducible methods for the assay of prolactin in the human. There is no doubt that the pituitary is essential to lactogenesis. When the lactating rat is hypophysectomized, no milk can be obtained 16 hours later by suckling rat pups.[6] It is further established that the anterior pituitary gland secretes a hormone with lactogenic properties,[19, 21, 27] prolactin, which is produced by the eosinophilic cells.[26] In the rat, these cells are increased by 3 days post partum almost 100 per cent over the number present in pregnant animals.[14] This increase appears to be due to conversion of chromophobe cells. The basophilic cells are not increased during lactation.

The mechanism of initiation of lactation is not entirely clear. Folley postulates that low levels of estrogen activate lactogenic function whereas higher levels inhibit it.[5] He suggests that progesterone, in the levels found in pregnancy, inhibits the lactogenic stimulus of estrogen, and the fall in the ratio of progesterone to estrogen at delivery releases this inhibition and the positive lactogenic effect of estrogen asserts itself. Recent evidence suggests that the hypothalamus may exert an inhibitory influence on the secretion of prolactin. Eckles and associates reported long-continuing lactation in women treated for breast carcinoma by pituitary stalk section with insertion of polyethylene plates between the cut ends.[13]

The Chiari-Frommel syndrome is presumed to result from either an increase in prolactin secretion or a disruption of an inhibitory factor which would normally prevent the eosinophilic cells from producing large amounts of prolactin. Until a reliable assay method for prolactin in the human is available, such considerations must remain highly theoretical. Some believe that prolactin and luteotropin are identical and report assays for prolactin on this basis, but this is questioned by others.[12]

A similar syndrome with amenorrhea and galactorrhea has recently been described by Argonz and del Castillo,[2] and Forbes and associates.[15] This syndrome differs from that of Chiari-Frommel in several respects. These cases were unrelated to pregnancy. They demonstrated a lower than normal follicle-stimulating hormone excretion in almost all of their cases, whereas this finding has not been consistent in the Chiari-Frommel syndrome. Of particular interest was the finding of evidence of pituitary tumor in many of these patients. Forbes reported 15 such cases, 8 of which had evidence of tumor, and in the 3 of these operated upon, a chromophobe adenoma was found. Forbes believes that all these cases, with or without tumor, have an overproduction of prolactin, so the fundamental mechanism of this syndrome and that of Chiari-Frommel may be the same. Lactation also occurs in acromegaly,[11] in which condition there is known to be an overproduction of hormone by the eosinophilic cells.

The one distinguishing feature of the Chiari-Frommel syndrome is that it occurs only immediately following a pregnancy. When the syndrome appears at this time, but in addition shows evidence of a pituitary tumor, it becomes indeed confusing as to how the case should be classified. Two such

cases[8, 17] have been reported. In the interest of clearer classification, it would seem preferable to classify such cases with those of Forbes and restrict the Chiari-Frommel syndrome classification to cases of postpartum amenorrhea, lactation, and uterine atrophy in which a pituitary tumor or other cause of abnormal lactation has been ruled out. It must be remembered as well that lactation has been reported in a variety of other conditions; following thoracoplasty and pneumonectomy, presumably due to stimulation of the same nerve fibers in the chest wall as mediate the suckling stimulus to lactation[25]; following encephalitis[10] and pneumoencephalography,[4] presumably on the basis of damage to the hypophysis or hypothalamus. It has also been reported following hysterectomy[24] and partial ovarian resection.[18] Chlorpromazine[5] and reserpine[20] have been reported to induce lactation, believed to be due to their action on the hypothalamus.

Summary

1. A case is reported which fits the Chiari-Frommel syndrome.

2. This is the nineteenth case reported of this syndrome, and the third in which a subsequent pregnancy has ensued.

3. Endocrinological considerations pertinent to this and other causes of abnormal lactation have been discussed.

4. This syndrome designation should be restricted to situations immediately following pregnancy in which no evidence of pituitary tumor or other cause of abnormal lactation is found.

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An evaluation of ureteroileostomy

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THE difficulties in providing an acceptable and functional reservoir or conduit for diversion of the urinary stream are attested to by the multiple methods devised and discarded as unsatisfactory. The utilization of nephrostomy, cutaneous ureterostomy, and multiple approaches to ureterointestinal anastomosis have been used with limited success.

Shoemaker,[12] in 1906, is credited with the first clinical report of application of diversion of the urinary stream to an isolated ileal loop. Bricker,[3] in a progress report published in 1952, outlined the results in 25 cases performed during the 2 preceding years. Since that time, he has published numerous articles describing in detail the technique, postoperative complications, and long-term follow-up on more than 100 cases. His results and an analysis of cases attest his success in revising and promoting this method which at the present time appears to be the most acceptable means of urinary stream diversion.

The interest of the gynecologist in such procedures has been expanded and extended through the reserved acceptance of radical and ultraradical operations promoted by Brunschweig and others in the treatment of certain malignancies of the female reproductive system. The success of total and anterior exenteration depends to a major degree on the mode of urinary stream diversion, which is not only superior in its functional and physiologic aspects but also in its esthetic acceptance to the individual patients.

Radical operation for pelvic malignancy has been performed in our institution by the gynecologic service for more than a decade. Initially, the ureters were transplanted into the sigmoid colon with the formation of either wet colostomy or mixing of the urinary stream and fecal streams with evacuation through the rectum. Frequent and progressive urinary tract infection as well as inability of patients to cope with a wet colostomy led us to seek a more satisfactory method of urinary stream diversion.

The resection of bowel and ureterointestinal anastomosis must be considered primarily in the realm of the surgical service. At the outset, pelvic exenteration was performed by a team consisting of a representative from the surgical, urologic, and gynecologic services, respectively. So formidable and multitudinous were the problems under this arrangement that it was unanimously agreed to seek a more satisfactory solution to this problem. Following several sessions at the departmental level, it was agreed that ileal bladder construction done in conjunction with exenteration for gynecologic malignancy should be the responsibility of the Obstetrical and Gynecological Service. In those patients having construction of the bladder as a primary procedure, this should be done by the Surgical Service. This has proved to be a satisfactory and harmonious arrangement.

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Table I

Case	Age	Date of operation	Diagnosis	Results
1. MW	49	5/2/56	Recurrent epidermoid to cervix	Living and well
2. DPJ	77	7/25/56	Carcinoma of the cervix with fistula	Dead
3. AW	26	7/15/57	Sarcoma of vagina	Dead
4. JB	60	1/28/58	Adenocarcinoma rectum	Dead
5. WB	50	2/3/58	Neurogenic bladder, post trauma	Dead
6. FBJ	59	5/6/58	Carcinoma sigmoid with metastasis	Living and well
7. JP	45	7/2/58	Transitional cell carcinoma of bladder	Dead
8. IMC	57	7/16/58	Carcinoma of cervix with fistula	Living and well
9. MG	11	8/5/58	Neurogenic bladder	Living and well
10. EH	51	11/12/58	Carcinoma of cervix, postoperative exenteration	Living and well
11. MLB	37	1/22/59	Neurogenic bladder, post trauma	Living and well
12. CBB	65	8/5/59	Post Wertheim ureteral obstruction	Dead
13. MJ	53	8/7/59	Carcinoma of cervix recurrent	Living and well
14. MW	40	8/26/59	Carcinoma of cervix recurrent	Dead
15. NW	47	9/1/59	Carcinoma of cervix with fistula	Dead
16. MS	58	9/16/59	Fistula with recurrent carcinoma	Dead
17. CPS	66	10/12/59	Transitional cell carcinoma urethra	Living and well
18. LM	63	11/18/59	Carcinoma of vagina	Living and well
19. HB	53	1/7/60	Neurogenic bladder, post trauma	Dead
20. EG	45	1/27/60	Carcinoma of cervix recurrent	Living and well
21. FWT	29	2/24/60	Postop (Wertheim) Post irradiation	Living and well
22. PC	38	3/2/60	Recurrent carcinoma of cervix	Living and well
23. DR	48	6/9/60	Urinary incontinence (scarring)	Living and well
24. BW	37	7/14/60	Carcinoma of vulva and vagina	Dead
25. JB	47	8/3/60	Primary carcinoma of vagina	Dead
26. JP	12	9/29/60	Lower urinary tract obstruction congenital	Dead
27. LR	49	10/19/60	Carcinoma of bladder	Dead

Material

This report constitutes an analysis of 27 patients, as recorded in Table I, who had diversion of the urinary stream into an isolated ileal loop during the period since July, 1956. In each instance, the operation was performed by one of the authors or under his direct supervision.

Indications for procedure

The indications for operation in this series are summarized in Table II. As noted, the treatment of carcinoma of the uterine cervix or the complications of therapy provided by far the most common indication.

Exenteration is done on our service in advanced cases of radioresistant or recurrent carcinomas and seldom as a primary procedure. One exception occurred in this series. The patient, a 51-year-old white woman, was subjected to subtotal hysterectomy elsewhere as therapy for a Stage II epidermoid carcinoma of the cervix. Exploration with proposed removal of cervical stump, vagina, and pelvic lymphadenectomy had to be extended to total exenteration due to extension of the carcinoma to the ureterovesical junction and parametrial area.

The case of progressive ureteral obstruction postoperatively occurred in an elderly patient who had radical hysterectomy performed one year prior to ileal bladder construction. It was apparent that obstruction occurred secondary to adherence of the ureters to the lateral pelvic wall. No evidence of recurrent carcinoma was found at the time of operation.

The selection of patients for operation with large vesicovaginal fistulas secondary to active cervical carcinoma is extremely difficult. In general, selection is based on the presence of limited recurrence in a patient whose activity is restricted primarily because of the leakage of urine. We would also like to believe that their life expectancy exceeded a minimum of 6 months.

Ileal bladder for diversion of the urinary stream prior to irradiation therapy in carcinoma of the urinary bladder has been reported by others.[9] Associated bladder infection with ascending pyelonephritis as well as ureteral obstruction provides the primary basis for this approach. Prevention of bladder tenesmus during therapy is largely eliminated.

Patients with a neurogenic bladder due to trauma or congenital defects, such as those associated with spina bifida and meningomyelocele, provide an excellent indication for diversion. The elimination of ascending infection and provision for an acceptable receptacle for urine is of obvious advantage.

Progressive bilateral ureteral obstruction with resultant reduction of renal function serves as an additional group in which ileal bladder may be utilized.

Technique

A description of our technique is important to the understanding of the problems and complications as analyzed in this series. No claim to originality is intended since Bricker[3] and others have previously described and illustrated a similar technique.

The careful selection of the site for emergence of the ileal stoma on the abdominal wall is important prior to operation. This must be determined in both the supine and upright positions. Factors to be considered are (1) adequate skin surface for attachment of the urinary receptacle, (2) sufficient distance from the groin to prevent interference with ambulation and from the midline incision to prevent spillage of urine and interference with healing of the surgical incision. A midline incision is preferable, particularly in those cases requiring abdominal wall ostia for both ileal bladder and colon, as it allows wide separation of the two. Adequate exposure is better achieved through the use of this incision.

Table II. Indications for operation

Total pelvic exenteration		11
Recurrent carcinoma cervix	4	
Carcinoma of large bowel	2	
Carcinoma of vagina	4	
Inadequate operation for cervical carcinoma	1	
Anterior pelvic exenteration		1
Radioresistant carcinoma cervix		
Neurogenic bladder		5
Congenital	2	
Posttraumatic	3	
Vesicovaginal fistulas		5
Recurrent carcinoma of cervix	3	
Presumed but not confirmed recurrent carcinoma of the cervix	1	
After irradiation and Wertheim operation	1	
Carcinoma bladder or urethra		3
Progressive ureteral obstructive uropathy (after radical hysterectomy)		1
Urinary stress incontinence secondary to lymphopathia		1

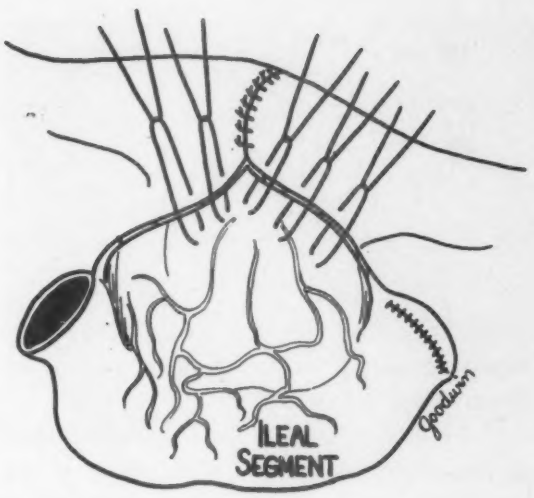


Fig. 1. Preparation of ileal loop.

Identification of the terminal ileum as it enters the cecum and selection of a segment with an adequate blood supply is the next step. The distance for the distal division is at least 2 inches from the ileocecal junction as this facilitates re-establishment of intestinal continuity following isolation of the proposed loop. Closure of the proximal end of the loop and repair of the mesentary is achieved as illustrated in Fig. 1.

It is necessary to provide an ileal segment of sufficient length to allow a generous segment to be pulled through the abdominal wall without torsion and subsequent interference with the blood supply and to prevent tension on the ureterointestinal anastomosis. A generous length of ileum to project well above the skin ostia and allow adequate re-

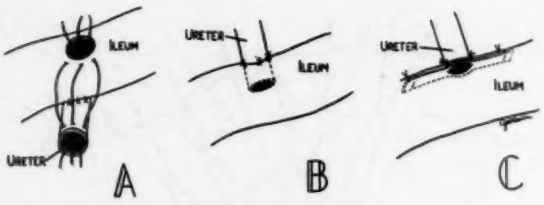


Fig. 2. Methods of ureterointestinal anastomosis.

vision following healing is also important. Mucosa-to-skin anastomosis of the abdominal stoma is not indicated.

Ureterointestinal anastomosis is performed as illustrated in Fig. 2. This phase of the procedure requires meticulous attention to detail but can be done accurately and rapidly if good exposure is maintained.

Illustration *A* in Fig. 2 demonstrates the most commonly acceptable and utilized method of anastomosis. Some degree of hydroureter facilitates this method that offers the advantage of a mucosa-to-mucosa union under direct vision.

Illustration *B* demonstrates blind implantation of a segment of ureter into the lumen of the ileal loop. Its disadvantages are apparent, and this type of implantation is best reserved for the rare case of ureteral obstruction due to edema, etc., in the immediate postoperative period.

In Illustration *C*, the ureter is divided longitudinally with fixation of the subsequently formed equal flaps through the wall of the isolated ileal loop. This method assures minimal manipulation and suturing in the immediate vicinity of the ureteral lumen and may be used in cases where there is minimal to no dilatation of ureter.

Perhaps the most important suture of all is that which fixes the serosa of the ureter to the serosa of the ileal loop proximal to the ureterointestinal anastomosis. This prevents or reduces the possibility of undue tension on the mucosa to mucosa anastomosis.

Care must be exercised to prevent ligation or perforation of a small vessel almost consistently present and intimately attached in the periureteral sheath. To further insure an adequate blood supply, the attachment of the ureter to the posterior parietal peritoneum is maintained except where absolutely necessary for mobilization.

Splinting of the ureters with ureteral catheters in the postoperative period serves no useful purpose. Removal of the appendix is done as an incidental procedure. We have found it unnecessary to close the right lumbar gutter to prevent internal hernia. Fixing the mesentery of the isolated ileal loop in the region of the ureterointestinal anastomosis is important to prevent herniation of small bowel as it happened in the case presented under "Mortality." This line of sutures also prevents tension on the ureterointestinal anastomosis.

Fig. 3 illustrates the completed operative procedure, and Fig. 4 is a photograph of the widely separated ileal and colic skin stoma.

Preoperative urography

As expected, hydroureter and hydronephrosis as well as the radiologic findings of chronic pyelonephritis were the most common findings on intravenous and retrograde urography.

The results of preoperative urography are as recorded in Table III.

Fig. 5 illustrates significant reduction in hydroureter and hydronephrosis following di-

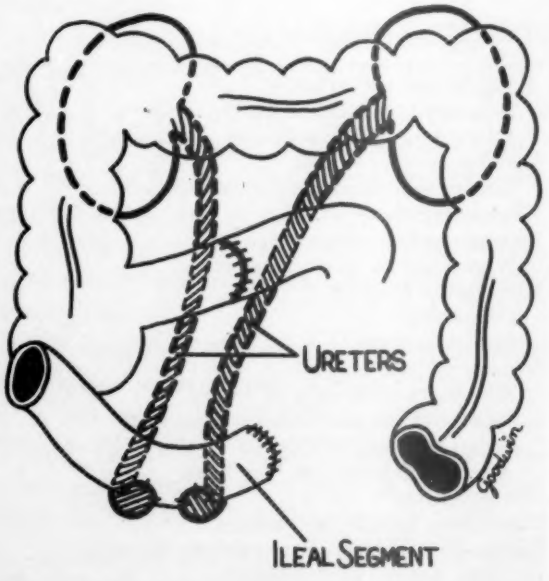


Fig. 3. Schematic illustration of completed procedure.

version of the urinary stream in a patient with a neurogenic bladder secondary to traumatic paraplegia.

Fig. 6 demonstrates improvement in dilatation of the urinary tract following total exenteration with ileal bladder for recurrent carcinoma of the cervix.

Postoperative complications

As expected, postoperative adynamic ileus was the most significant problem in many cases. The usual preventive and supportive measures in the treatment of ileus was effective in combating this complication. Infection was of importance only in those cases with extensive tumor necrosis or existing infection due to other causes at the time of operation. Quantitative electrolyte determinations were done repeatedly but in no instance was there any significant alteration thought to be due to reabsorption from the isolated ileal loop.

Ureteral obstruction in the immediate postoperative period occurred on two occasions. In both cases, re-exploration was done; one 4 hours after the procedure with no abnormality found; the other 48 hours after the initial operation. The latter case is presented in more detail:

L. M., a 63-year-old white woman, was admitted to the hospital on Nov. 9, 1959, for treatment of an epidermoid carcinoma of the vagina. Examination revealed a fungating lesion of the posterior vaginal wall extending from the cervix almost to the hymenal ring. On Nov. 18, 1959, she had a radical vulvectomy and groin dissection as well as total pelvic extenteration with construction of an ileal bladder.

Postoperatively, she had intermittent episodes of hypotension and oliguria. After stabilization of blood pressure and adequate hydration produced no significant increase in urine excretion, re-exploration was performed 48 hours following completion of the original procedure.

At operation, both ureters were obstructed by edema and hemorrhagic material occluding the lumen at the site of the anastomosis. Revision of the anastomosis was achieved by implantation of the distal 1 cm. of the ureter into the isolated ileal segment. Urinary excretion was immediate and continued without any further problems.

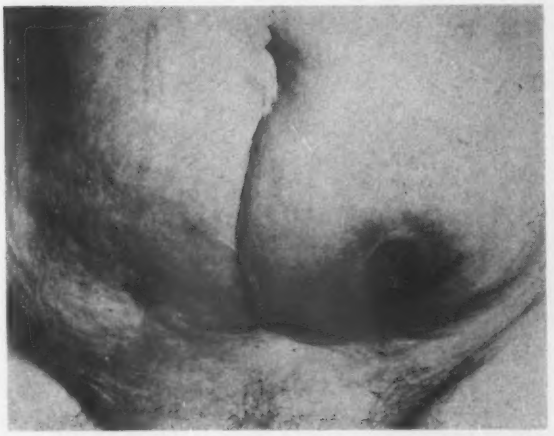


Fig. 4. Abdominal wall with bladder ostium on right, colon ostium on left.

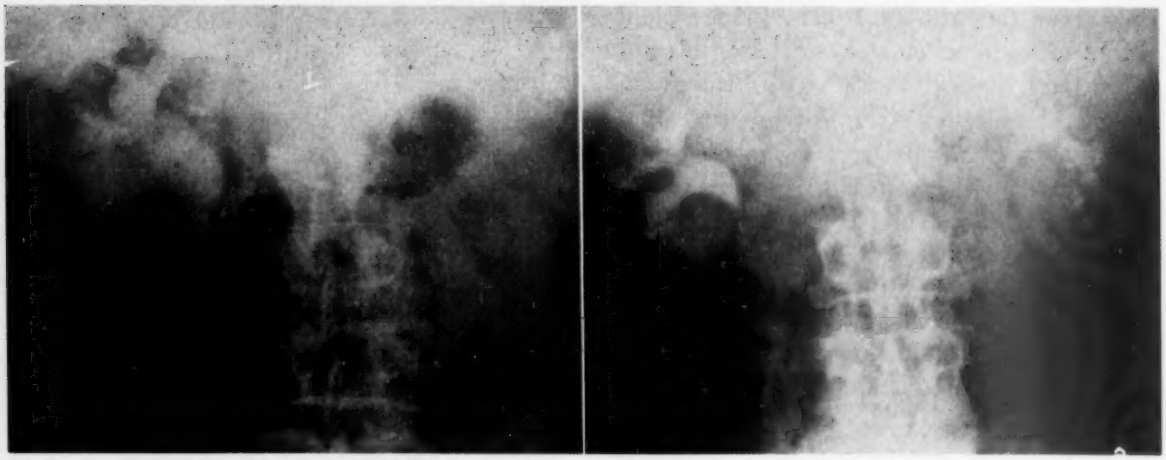
Mortality

There were 4 surgical deaths, defined as death within 30 days following operation, in this series. Our surgical mortality rate of 15 per cent compares favorably with that of 14 per cent reported by Bricker,[5] and is significantly less than the 30 per cent reported by Wells[15] and 25 per cent in the series reported by Annis.[1]

Two of the 4 deaths should be discounted since in one instance death occurred during the operation and was due to uncontrolled hemorrhage at the time of total pelvic exenteration. The other was due to Gram-negative *(Escherichia coli)* septicemia 36 hours after total exenteration for carcinoma of the vagina.

One of the deaths is worthy of comment since it represents an important technical error.

D. J., a 77-year-old Negro woman, was admitted to the hospital on July 23, 1956, for evaluation and treatment of vesicovaginal and rectovaginal fistulas. Past history revealed that she received irradiation therapy for a Stage I (League of Nations) epidermoid carcinoma of the cervix in 1949, 7 years prior to admission. Preoperative evaluation revealed a remarkably preserved woman of apparently stated age and a satisfactory candidate for the proposed surgical procedure. Multiple biopsies in the region of the fistulous tracts showed no evidence of carcinoma. Construction of an ileal bladder was performed without difficulty on July 25, 1956.



A B

Fig. 5. Case 19. *A*, Preoperative urography; *B*, postoperative urography.

The postoperative course was remarkably benign, the nasogastric suction was removed on the fourth postoperative day and the sutures on the seventh day with the incision noted to be well healed. On the twelfth day the patient was noted to be lethargic, with increasing abdominal distention and decreasing urinary output. The ileal stoma was noted to be gangrenous and there were signs of generalized peritonitis. Surgical exploration performed on the twelfth day revealed a large noninfected hematoma in the lower portion of the previous surgical incision. A small abscess produced by a leak at the site of the ileoileal anastomosis was encountered. A disruption of the ureteroileal anastomosis had occurred due to herniation of the jejunum posterior to this anastomosis. Cardiac arrest and death occurred during the procedure.

Comment. Prevention of these complications could have been achieved by consideration of potential problems as described under Technique.

Results

Thirteen of the 27 cases of diversion of the urinary stream by the isolated ileal loop technique have been evaluated at variable periods following the initial operation. Our survival rate of only 45 per cent may seem unreasonable but on closer analysis the extensive primary disease or its recurrence provided the basis for this high mortality. In only one instance was construction of the ileal bladder the real basis for postoperative mortality.

Table III. Preoperative urography

Normal pyelograms	11
Radiologic findings indicating chronic pyelonephritis	3
Bilateral hydronephrosis	3
Unilateral hydronephrosis	5
No preoperative or unsatisfactory pyelography	4
Nonfunctioning right kidney	1

Electrolyte studies recorded in Table IV on patients available for study at this time demonstrate a slight and insignificant hyperchloremic acidosis. Blood pH studies and the absence of subjective symptoms in these patients indicate that this abnormality is of little clinical importance.

The studies in Case 13 are of limited value since this patient is now in a terminal state because of recurrence of the carcinoma.

The acceptance and accomodation of the patients to this form of urinary diversion has been gratifying. Even the 12-year-old child has assumed an integrated existence among her contemporaries that was impossible prior to control of urine.

Comment

Isolation of an ileal loop with the formation of a urinary conduit as advocated by Bricker provides at this time the most acceptable method of diversion of the urinary stream.

Advantages of this method include reduction of back pressure or reflux by the wide-open external stoma. The technique of mu-

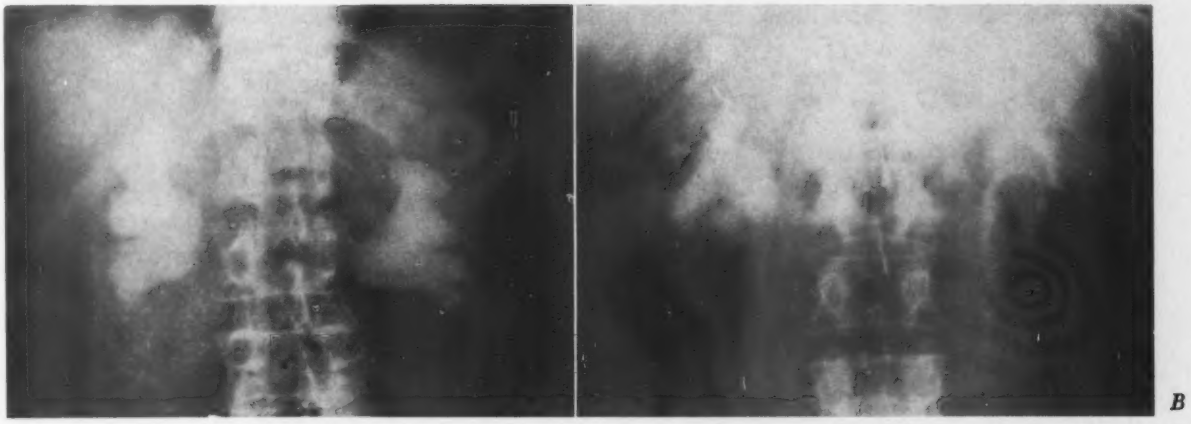


Fig. 6. Case 1. *A*, Preoperative urography; *B*, postoperative urography.

cosa-to-mucosa anastomosis provides visual confirmation of patency and minimizes postoperative ureteral obstruction. Peristalsis in the isolated ileal segment prevents stagnation of urine.

Absorption from the ileal segment is clinically insignificant as demonstrated in this series. This confirms the studies of Bricker[3] in that electrolyte disturbance is not a problem.

Stamey and Scott[13] found no evidence of diuresis from urea absorption or chronic potassium loss in 14 patients. Eiseman and Bricker[7] showed by infusion of ileal segments that both chloride and urea are absorbed appreciably, but clinically they did not find this absorption to be a problem. Pyrah[11] demonstrated that colonic mucosa absorbs chloride in excess of sodium ions. Of even more significance was the finding that sodium, chloride, and potassium ions migrated across the mucous membrane of the ileum in equal amounts.

Klinge and Bricker[9] found the average segment fluid volume emptied at one time in the supine position is highly constant between 56 and 63 per cent of the total volume.

No improvement is PSP and creatinine clearance following diversion of the urinary stream in patients with carcinoma of the bladder was found by Levin. He did find BUN, serum creatinine, and improvement in intravenous pyelography results but little change in the urine bacteriology. His data also indicate more compromise of renal function due to chronic infection and obstruction than had previously been appreciated. These findings serve to illustrate the importance of preventing ascending urinary infection by separation of the fecal and urinary streams, particularly in those patients with compromise renal function prior to operation.

Of utmost importance is the provision of a method of urinary stream diversion that is acceptable to the patient. Use of the Rutzen bag, the Lapides device, and the Con-Seal enterostomy allow emptying the urine collection at frequent intervals without detaching

Table IV. Electrolyte studies (serum)

Case	*Time after operation*	*Blood pH*	*Osmolarity (mOsm.)*	*Total protein (Gm. %)*	*Sodium (mEq./L.)*	*Potassium (mEq./L.)*	*Chlorides (mEq./L.)*	*BUN (mg. %)*	*CO_2 (vol. %)*
10	2 years	7.340	282	6.88	151.3	4.00	106.9	12.0	54.1
22	1 year	7.320	295	6.58	149.5	4.10	102.6	16.5	50.8
18	2 years	7.350	298	8.10	147.8	3.90	105.1	13.0	54.1
13	2½ years	7.310	277	7.76	128.6	3.90	92.8	24.5	49.1
23	8 months	7.1560	290	6.58	139.2	4.21	101.8	12.0	67.3
1	5 years	7.250	292	6.99	146.0	4.51	107.4	19.5	58.6

the device and with subsequent decrease in the offensive urinary odor.

Summary

1. The results of the isolated ileal loop as a method of urinary stream diversion has been evaluated in 27 operations performed since 1956.

2. The indications for this procedure have been described.

3. Electrolyte studies and intravenous pyelography have demonstrated its effectiveness in providing a satisfactory urinary conduit.

4. Certain technical problems related to the procedure have been presented.

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Discussion

DR. W. NORMAN THORNTON, JR., Charlottesville, Virginia. It would be wise in discussing the application of the ileal segment method of urinary diversion to separate the patients into groups according to whether the method is applied as a primary procedure or in association with anterior or total exenteration. The technical difficulties and operative and postoperative complicatons are necessarily greater than when the ileal conduit is constructed as the primary and only procedure.

We would prefer the mucosa-to-mucosa ureteroileal anastomosis as advocated by others. The distal end of the ileal loop is brought out through a true circular defect, passing through all the abdominal layers as advocated by Stamey and Scott (Surg. Gynec. & Obst. 104: 11, 1957). I believe this step is important in minimizing the chances of strangulation of the mesentery or subsequent constriction of the loop within the abdominal wall.

Our experience with upper urinary tract infections occasioned by constant presence of feces in the wet colostomy or with ureterosigmoidostomy would indicate that diversion of the fecal stream is essential if we wish to achieve long-term survival with ureterointestinal anastomosis. Construction of a sigmoid colostomy with isolation of the rectal ampulla to function as a bladder with control of urine by the anal sphincter has been utilized as a method of diversion of the fecal stream. In our experience, this was not satisfactory as the patients had little control of urine during sleeping hours, although continent during the day.

We would agree that, although a poor substitute for an intact normal urinary system, the ileal conduit would seem to be the best substitute at present. However, long-term evaluation of this method of urinary diversion is necessary to evaluate its effectiveness in avoiding electrolyte imbalance and pyelonephritis. These are problems of special significance in the treatment of congenital anomalies and benign disease. Bricker and collaborators (Ann. Surg. 152: 388, 1960) reported this method of urinary diversion was responsible at least in part for 3 of 15 postoperative deaths among 150 women treated by exenteration for cervical cancer, and 2 other patients died from renal complications occurring after leaving the hospital. He also reported that 11 of 135 women surviving the operation have had recurrent pyelonephritis. Five additional patients dying of recurrent cancer developed pyelonephritis terminally.

On two occasions we have utilized an ileal

segment as a substitute for the distal portion of the ureter in association with ureterovaginal fistulas following radical hysterectomy for carcinoma of the cervix. In both patients it was not possible to reimplant the injured ureter into the bladder. In one patient a right ureteroileoneocystotomy was done and in the other bilateral ureteroileoneocystotomy was accomplished. One patient has been followed for 18 months and the other for 2 years. Pyelograms show essentially normal upper collecting systems in both patients, but a much longer follow-up is necessary to evaluate this method of ileal substitution for a portion of the ureter.

DR. WALTER L. THOMAS, Durham, North Carolina. The isolated ileal segment used as a urinary conduit has brought to the gynecologist and especially to the urologist a renewed interest in urinary diversion. It has given to the patient a new hope for longer life and a less miserable form of existence. The great virtue of ureteroileostomy is that it permits drainage of the kidney and preserves that always vital renal function without the use of catheters.

Ureterosigmoidostomy, especially for the anterior exenteration, is still the preferred initial urinary diversion in my judgment. "I just don't like my excrements draining from my abdominal wall." There are three main complications following ureterosigmoidostomy: pyelonephritis, hyperchloremia, and obstruction due to stenosis at the anastomoses. The first can be prevented by a prophylactic antibiotic; the second can be checked by a dose of sodium bicarbonate daily; there is no protection against stenosis that I know of except good surgical technique and luck. Should the ureterosigmoidostomy go bad, before that precious renal function has been lost, the ileal loop can be done.

We have always considered urinary diversion at Duke University as primarily in the realm of the Urological Division. We do join the team when the woman is one of our gynecologic patients. There have been 49 such procedures carried out on our patients.

There are a few things which we feel should be emphasized in the technique. The careful selection of the site for the ileal stoma has been emphasized by Dr. Dennis. We feel that this selection is greatly enhanced by having the patient actually wear the collecting bag for 2 to 3 days prior to the procedure. The individual body configuration, obesity, etc., make a difference. In other words, the patient helps select the site by actual practice.

The ileal loop should be adequate but not too long; it should be thoroughly anchored, and placed retroperitoneally. This minimizes postoperative complications.

Two points in the after care—we have found the most satisfactory collecting bag to be the Perma Bag (Eastern Laboratories, Hartford, Connecticut). Skin reactions are held to a minimal by always using alcohol after the benzene solvent used to cleanse the skin. This neutralizes the benzene.

Finally, it is only through such efforts and observations made by Dr. Dennis and others that we will better understand the exact indications and value of ureteroileostomy. Our group feel that we are learning all the time.

We believe that in the final analysis from a gynecologic viewpoint any type of urinary diversion should be classified as a "desperation operation"—desperation because of the delay in early diagnosis and adequate treatment.

Studies in human myometrium during pregnancy

II. Resting membrane potential and comparative electrolyte levels

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With the technical assistance of
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THE mechanism by which the myometrium is maintained in a quiescent state during pregnancy and then becomes activated during labor is not clearly established. Most of the studies concerned with myometrial changes at a cellular level have been carried out in animals and may not necessarily be applicable to human gestation. In view of the basic necessity of proper electrolyte concentration for muscular contraction, we have been studying the ionic profile of human myometrium in pregnancy, comparing the placental with antiplacental sites with the idea that placental progesterone might be exerting a local effect on the overlying myometrium.

In a previous report of this work[1] we have shown a marked difference between these two areas of the myometrium. The electrolyte levels of the placental versus the antiplacental sites are quite different, with a difference which shifts as pregnancy progresses. In that study, however, we were unable to report what portion of the tissue ions were intracellular due to the lack of the available techniques applicable to smooth muscle tissue, and hence could not arrive at the theoretical resting potential values. The determination of resting potential would help explain the higher total tissue potassium at the placental site in the myometrium of human subjects[1] and animals[2] at certain stages of pregnancy since resting potential is mainly dependent directly on the intracellular potassium concentration. The resting potential levels are also important in the function of the muscle cells since they control the contractility during resting and active phase. Accordingly, direct measurements of resting potential have been undertaken, and the present report deals with these measurements as well as with further determinations of the tissue electrolyte levels.

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Material and methods

Specimens from 24 pregnant patients, at various stages of pregnancy, were obtained from the myometrium overlying the placental and antiplacental sites. The clinical episodes included therapeutic abortion, elective repeat cesarean section, and cesarean hysterectomies. The biopsy material was transferred to the laboratory where the tissue was blotted free of superficial blood. In the last 7 cases, a small strip of muscle was obtained for the measurement of resting potential while the rest of the specimen was used as described previously[1] for the electro-

lyte estimations. The strips of muscle for resting potential measured somewhere from 3 to 3.5 cm. in length and 1 to 1.5 mm. in width and thickness, and were kept in Ringer-Tyrode solution oxygenated with 95 per cent oxygen and 5 per cent carbon dioxide. It was initially determined that the keeping of these strips in Ringer-Tyrode solution did not affect the resting potential significantly if the recordings were obtained in less than 4 hours' time. All of the recordings reported here, however, were completed within 1½ hours from the time of obtaining the specimen.

The resting potentials were recorded using the external electrode technique of Stämpfli[3] with some modifications. This technique is based on the assumption that the full value of the membrane potential can be measured with external electrodes on a core conductor when the short circuiting is negligible. The short circuiting was eliminated by increasing the outside resistance of the preparation in the interpolar region by replacing most of the ions in the interstitial fluid with nearly ion-free sucrose solution. The ion-free sucrose solution was made with distilled water which was passed through an exchange resin column. The depolarization was done by 100 mM. potassium sulfate solution. The bath chamber was made according to the modification of Sperelakis.[4]

The stock solutions were kept in a constant temperature bath and were oxygenated with 95 per cent oxygen and 5 per cent carbon dioxide. The actual temperature of the chamber was 31° C. and the three solutions in the chamber were continuously replaced by a constant siphon. It was thought necessary to keep the temperature constant in all of our recordings, as was the tension, the latter being measured by a force and displacement transducer (Statham Instruments, Inc., model G10B—0.3-350) connected to a Sanborn strain gauge amplifier (64-500B) and Twin Viso pen recorder. The electrodes used for recording were Ag/AgCl sodium chloride electrodes.

It must be emphasized that we do not claim absolute values for resting potentials, but a relative correlation between the pla-

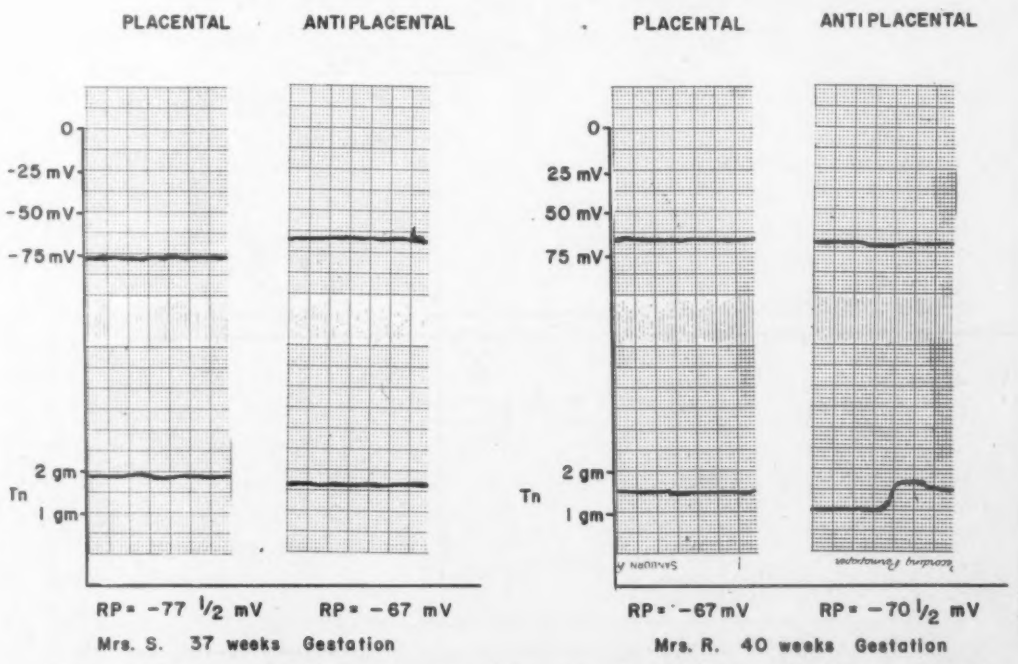

Fig. 1. Resting potential determinations of muscle strips from the placental and antiplacental sites of two patients, one at 37 weeks of pregnancy and the other at term. In the former, a significant difference is noted between these two areas whereas at 40 weeks there is no difference in resting potential.

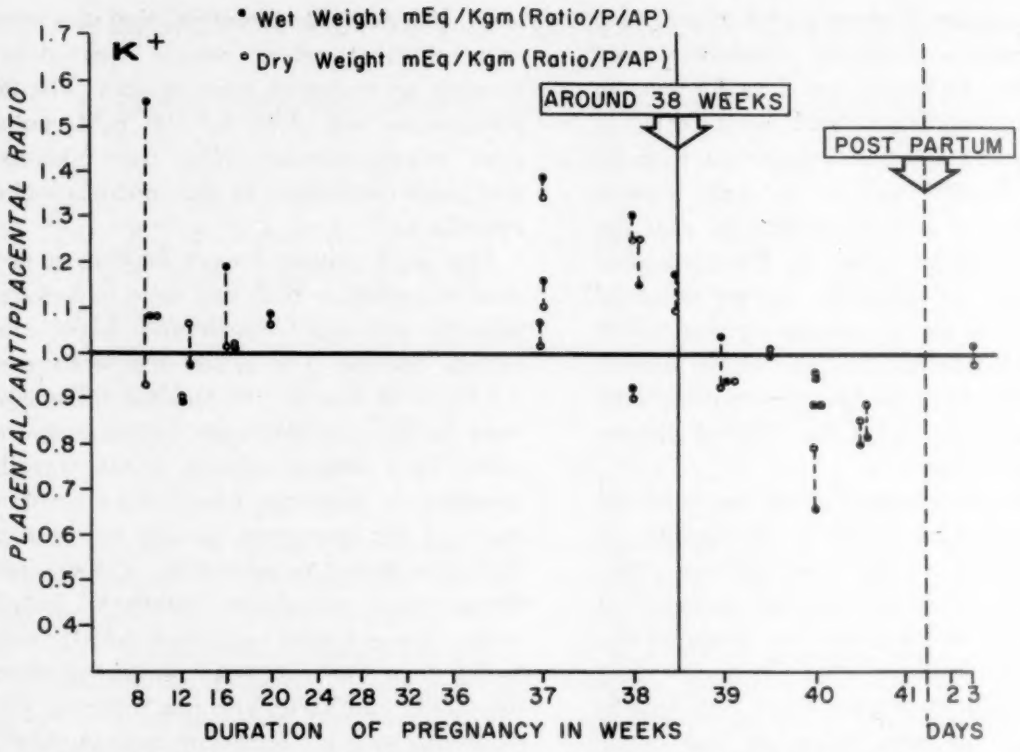

Fig. 2. Tissue potassium levels expressed as the ratio of the amount per kilogram at the placental site divided by the amount at the antiplacental site. The mean value of this ratio rises throughout pregnancy and then drops at term to below 1.

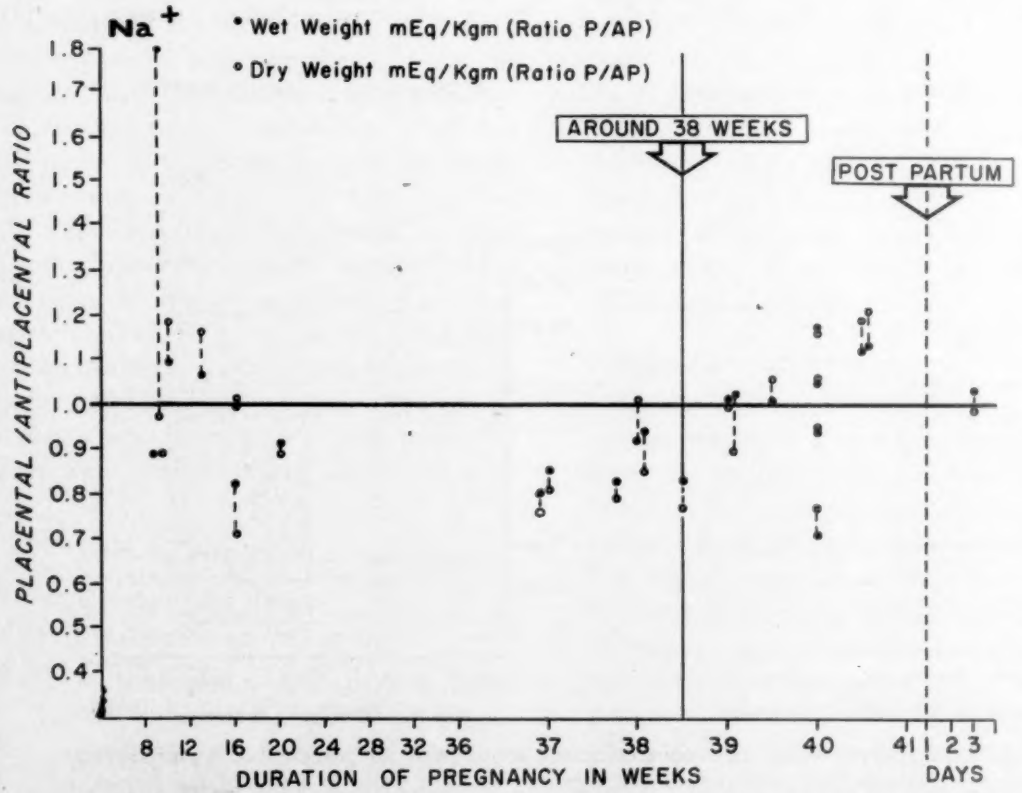

Fig. 3. Tissue sodium values also expressed as the ratio, placenta site level divided by antiplacental site level. It can be seen that the trend is the opposite of that observed with potassium.

cental and antiplacental myometrial strips was possible when the determinations were done under identical circumstances. Any difference of less than 5 mV. between these two sites was considered insignificant.

Results

Resting potential recordings in pregnancy showed an interesting trend corresponding with the theoretical predictions, based on the potassium concentration difference at these two sites.[1] The resting potentials in all the 5 cases at, or before, 38 weeks revealed higher recordings at the placental than at the antiplacental site. Two cases after 38 weeks' gestation—one at 39 and another at 40 weeks' gestation—showed very little difference in the resting potential at these two sites. The recordings from these two different sites are shown in Fig. 1.

Further studies on electrolytes in human myometrium include 15 new cases and a review of the 9 previously reported cases.

As shown in Fig. 2, potassium ion concentration has continued to show the trend noted previously.[1] At the placental site, the total tissue potassium concentration when expressed in milliequivalents per kilogram of wet and dry weight tissue is higher at the placental site than that from the antiplacental site, up to around 38 weeks of gestation. This trend, however, is not very significant in the first trimester of pregnancy. After 38½ weeks of gestation, until term, this difference seems to disappear and in the majority of cases the potassium concentration at the placental site is either somewhat lower or the same as it is at the antiplacental site. One biopsy from a 3 days' postpartum uterus showed no difference in these two sites. Total tissue chloride and sodium levels reveal just the opposite trend when compared with the potassium concentration as shown in Figs. 3 and 4, respectively. The water content at these two sites does not show significant difference.

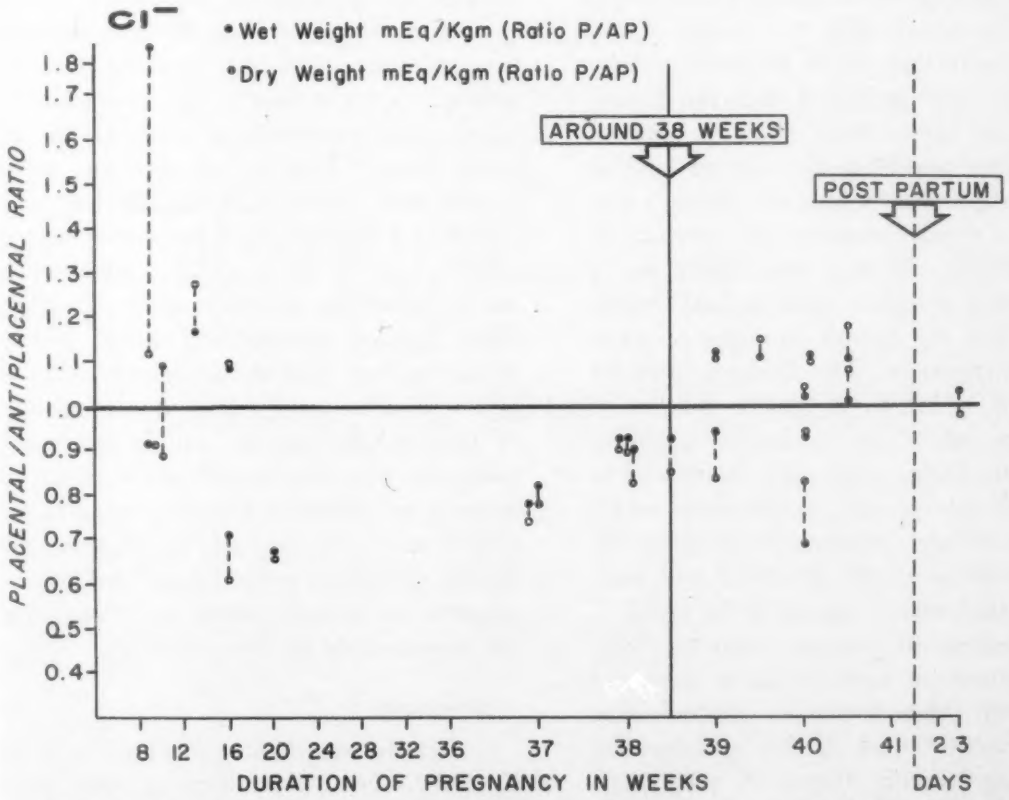

Fig. 4. The chloride findings parallel those of sodium with the ratio of the placental to antiplacental sites below unity until near term when it is reversed.

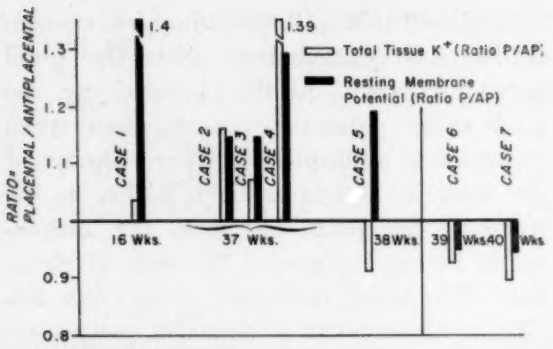

Fig. 5. The resting membrane potential of the two areas under study is here expressed as the ratio of that found in the placental site to that found in the antiplacental myometrium. In the determinations of early pregnancy this ratio is well above 1, whereas (like the potassium ratio) it drops below 1 between the thirty-eighth week and term.

Comment

The knowledge of transmembrane resting potential, which is the result of the ionic gradient across the cell membrane, is essential in the understanding of muscle cell function, since this potential controls myometrial contractility during both the period of rest and the contraction phase. Studies on skeletal muscle have indicated that the resting potential is higher than it is in smooth muscle, thus providing the former with a larger margin of "membrane safety" and requiring a greater stimulus for contraction. Smooth muscle, on the other hand, has a lower resting potential than skeletal muscle and thus has the unique property of spontaneous rhythmicity. The findings reported here would point to a greater margin of "membrane safety" in the muscle overlying the placenta during pregnancy (compared to the rest of the uterus); a difference which disappears as labor approaches. At term, the resting potential in the placental and antiplacental sites would appear to be equal.

The findings in humans reported here, and of others in animals, have shown a higher total tissue potassium concentration at the placental than at the antiplacental sites during certain stages of pregnancy. Progesterone, experimentally in animal uterus, has also been shown to increase the total tissue potassium concentration. However, whether or not this increase in total tissue potassium is in the intracellular compartment has not been determined. Our data on resting potential have thrown some light on this question. Fig. 5 reveals that the higher values of resting potential are concomitant with the total tissue potassium rise at the placental site in at least 4 out of 5 cases. Since the resting potential is mainly dependent directly on the potassium concentration present inside the cell, it might be assumed that this rise of total tissue potassium at the placental site is the reflection of the intracellular potassium increment.

Since it has been demonstrated in the laboratory animal that progesterone can exert an effect on the myometrial electrolyte content,[2] it has been assumed that this represents the mechanism of action of progesterone. Csapo[5] points out that progesterone given experimentally to rabbits raises the resting potential above that found in an estrogen-dominated uterus and thereby decreases the spontaneous activity with a loss of conduction and loss of pharmacologic responsiveness. Daniel,[6] working with the uterus of cats, came to the conclusion that in vivo the myometrium overlying the placenta showed little or no electrical activity before term and would usually fail to respond to intramuscular injections of oxytocin (0.025 to 0.25 unit) which would activate the myometrium in other areas. No studies from human myometrium have thus far been reported, and the assumption that the observed differences represent a local effect of progesterone on the muscle tissue overlying the placenta (a difference which disappears as placental function declines near term) must remain an assumption. Our studies of action potential in vivo, now in progress, in human pregnant uterus, might throw some light on this problem.

Summary

1. Resting membrane potential and Na, K, and Cl levels have been reported in human pregnancy myometrium.

2. Up to around the thirty-eighth week of

gestation, the resting potentials and total tissue potassium levels are higher at the placental than at the antiplacental site. After the thirty-eighth week, and up to term, a shift takes place so the two areas are equal.

We wish to express our appreciation to Mr. Herbert Stran for his advice and assistance in obtaining the resting potential measurements.

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Septic shock in obstetrics and gynecology

Bacterial shock complicating acute Bartholinitis

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MEDICAL and nursing attendants alike must remain alert to the possibility of unusual complications. Since a common illness is expected to run a perfectly benign course, initial neglect may occur because so many of the previously cared for and apparently similar cases presented no problem in diagnosis or treatment. Management of the aborting patient, for instance, rarely involves a sequence of potentially fatal complications, even though infection becomes apparent in approximately one third of the patients with abortions who are hospitalized. Barely less than one per each hundred of women with infected abortions who are hospitalized die, however, and this is in spite of the effective measures now universally available.

Knapp, Platt, and Douglas[6] have classified infected abortions into three groups according to the clinical manifestations of the infection. Recommended management varies with the type of infection. One third to one half the deaths which ultimately result now seem associated with the development of so-called septic or bacterial shock. Nowhere is the value of an alert examiner and the need for an accurate diagnosis more evident, or the futility of ineffectual treatment more striking, than is evidenced in the management of this unusual but frequently fatal syndrome.

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Studdiford and Douglas[9] were the first to call the attention of the obstetrician-gynecologist to the critical state of these patients almost as soon as recognition of their condition was possible and to the therapy indicated in this syndrome. Tenney, Little, and Wamsteker[10] and, more recently, Haugen and Roden[5] have reported somewhat similar circumstances preceding deaths in septic abortion associated with acute adrenal insufficiency. Haugen and Roden suggest that the so-called septic or bacterial shock of septic abortion and the state of the patient with acute adrenal insufficiency may appear clinically to be one and the same entity.

For more than a decade, circulating toxins produced by the colon-aerogenes group of bacteria have been known to produce vasomotor disturbances likely to terminate in irreversible shock. In 1952, Wise, Shaffer, and Spink[11] had reported 53 cases observed at the University of Minnesota Hospitals in which positive blood cultures were due to gram-negative organisms. In 1956, reviewing 137 cases of bacteremia due to gram-negative bacilli at the Mayo Clinic, Martin and Nichols[7] had noted a significant degree of hypotension in only 7 cases. They did observe, however, that, in all 7 of the cases in which evidence of bacterial shock developed, the infecting organisms were of the colon-aerogenes group. The latter have suggested (1) that a deadly degree of hypotension may supervene at any time during the course of infection by gram-negative organisms, (2) that treatment during the period of hypo-

tension must result in restoration of the circulation before renal ischemia persists long enough to produce renal damage, and (3) that, after circulation has been restored and if oliguria and rising concentrations of urea and potassium are noted and organic renal damage is evident, only meticulous management over a period of weeks will enable the patient to survive until renal function has been partially restored.

During the past year, within the obstetric-gynecologic services of the hospitals affiliated with this department, 4 more or less typical instances of severe bacterial shock have been observed. Three of these infections were obviously complicating abortions in the second trimester of pregnancy, and 2 of the 3 patients died. The nature of the problem was certainly recognized more promptly in the most recent abortion where this syndrome developed, for this patient exhibited the classical picture as described by Studdiford and Douglas[9]—initial vomiting and diarrhea, little bleeding, only "slightly bloody discharge," high fever, chills, then virtual disappearance of blood pressure and prolonged anuria. Circulation was maintained with a continuous drip of metaraminol; no transfusions were needed, but digitalis and antibiotics were given. It has been postulated that the chances for recovery of this particular patient may have been increased by the judicious use of anticoagulants early in the development of the hypotension.

It has been our impression that the clinical manifestations of bacterial shock and the therapy indicated are now so generally recognized there is little to be gained by reporting additional cases. The unusual etiology and course of a fourth case, however, as well as the heroic measures necessary to support the patient through a series of more or less typical complications, have prompted the following case report:

B. B., a 26-year-old white woman, gravida iv, para iv (1 stillbirth at term) was admitted to the Sisters of Charity Hospital on Dec. 2, 1960.

On May 13, 1960, at the time of the first prenatal examination in the fourth pregnancy, physical examination was essentially negative. A small, nontender, apparently cystic enlargement of the Bartholin gland was noted on the left side. This had not been present at the postpartum examinations following the third pregnancy. It did not enlarge, become tender, or disappear during the fourth pregnancy.

From May to October, 1960, nothing unusual had been noted, but cessation of fetal movement was reported one week before the expected date of confinement. The patient had then been admitted to the Children's Hospital on Oct. 26, 1960 and rapidly delivered a macerated stillborn infant. Fetal death seemed explained by 3 lengths of cord tightly looped about the fetal neck. The early puerperium was uneventful and she was seen for a postpartum examination on Dec. 2, 1960. Examination again seemed essentially negative. The left Bartholin gland was again noted to be palpable, nontender, evidently cystic, and unchanged. Since this enlargement had persisted throughout pregnancy and the puerperium, its removal was advised but no definite arrangements were made for operation. On December 1, approximately 12 hours before admission to Sisters Hospital, she had telephoned to report increased swelling and tenderness of the left labia. Hot sitz baths or hot packs were advised. On December 2, in the early morning, she again telephoned to report weakness, a shaking chill, diarrhea, greenish emesis, and a temperature of 106° F. She was immediately admitted to the hospital.

Physical examination revealed a well-developed but cyanotic woman in an atypical shock-like state, temperature 105° F. (rectal), blood pressure 82/40, pulse 140, and respirations 30. The lungs were clear; tachycardia was noted but no murmurs. There were hypoactive bowel sounds; no abdominal organs were palpable, and there were no distention or localized or rebound tenderness. Pelvic examination was essentially negative except for the left labia, which appeared hyperemic and edematous with thin purulent drainage from an apparently recently ruptured abscess of the left Bartholin gland. The patient and nurse thought that the rupture of the abscess had occurred after admission to the hospital, during the shaving and surgical preparation of the perineum and vulva. The tender, abscessed gland was apparently draining into the introitus by way of, or adjacent to, the site of the duct. There had been a noticeable

Table I. Daily laboratory determinations in a patient with bacterial shock

Day	*Urinary output (c.c.)**	*Na+*	*K+*	*Cl-*	*CO_2 combining power*	*BUN*	*Hemato-crit*	*Hemo-globin*	*White blood cells*
1st	75						46	14	5,600
2nd	305	138	4.8	109		30	45	13	30,200 (65 stab cells, 23 segmented cells, 12 lymphocytes)
3rd	190	138	5.3	110	23.4	54			
4th	325	137	4.7	104	24.3	60	35	9.8	
5th	290	138	5.2	110	22.5	60			
6th	285	133	3.9	111	21.2	81			
7th	595	133.4	4.3	101	18.0	92	36	11.6	3,400
8th	940								
9th	1,025	136	5.3	96	18.5	124	24	7.0	
10th	2,050	140	5.7	104	26.1	147	28	8.2	Fibrinogen 0.32 per cent Platelet count 108,000
11th	over 3,000	136	6.4	98	21.2	143	24	8.2	
12th	over 3.000	138	6.3	102	27.4	112	29	9.0	8,650
13th	over 3,000	144	7.4	102	23.8	120	25	8.0	
14th	over 3,000						34	10.7	
Discharge, 26th day		134	4.8	106	22.5	17	28	8.2	10,050

*Intake limited to 500 c.c. plus volume of urinary output—of 5 per cent glucose in water daily until tenth day when diuresis was evident.

tendency of the abscess to extend anteriorly and it had seemed to be pointing almost suprapubically; however, appreciable rupture and the only drainage approximated the site of the duct (Table I).

Course.

Immediate. Fluid from the draining left Bartholin abscess and blood was taken for cultures. Levarterenol in dosage sufficient to maintain systolic pressure between 90 and 100 was administered by continuous drip and 1 Gm. chloramphenicol and 1 million units of aqueous penicillin were given intravenously.

First day. Continuous levarterenol plus digitalis was given. The patient had two episodes of "coffee ground" emesis.

Second day. The patient's temperature did not rise above 99° F. The neck veins were distended and the liver tender. Levarterenol continued to maintain systolic pressure. Input of fluids was limited. Cultures reported *Escherichia coli.*

Third day. Administration of levarterenol was stopped at intervals. The systolic pressure was maintained about 90.

Fourth day. The blood pressure was lower; 100 mg. of hydrocortisone succinate in 500 c.c. of 5 per cent glucose in water was given.

Fifth day. Condition remained about the same. Dialysis was considered but thought to be not yet indicated.

Eighth day. At 10 A.M., the patient had an episode of vomiting with bright red clots. Bleeding from the nose was stopped with a nasal pack. Blood pressure was 120/80.

Ninth day. Hemoglobin loss was believed to be due to epistaxis; one pint of fresh blood was given. In the evening, the patient had emesis of 200 c.c. of "old blood" and had 200 c.c. of tarry stool. The blood pressure was stable. Three hours later, there was emesis of 600 c.c. of clotted blood. The diagnosis of "stress ulcer" was entertained. It was also considered that the gastrointestinal bleeding might be on the basis of uremia. A second transfusion was given.

Tenth day. In the early morning, the patient again had emesis of blood (400 c.c.) and 250 c.c. of tarry stool. Edema of the left eyelid was relieved with diphenhydramine. Later, there was emesis of 500 c.c. of clotted blood.

Eleventh day. Barium studies suggested a duodenal ulcer. There was more emesis of clots.

Thirteenth day. At operation, several bleeding ulcerations in the duodenum were noted and ligated. A vagotomy was performed. *Twenty-five pints of blood had been given between the ninth and the thirteenth hospital day.*

Subsequent course. The remainder of the course was uneventful except for skin grafting in areas of levarterenol infiltration of the left arm. Phenolsulfonphthalein excretion prior to

discharge: first sample, zero; second sample, 12 per cent; third sample, 20 per cent; total, 32 per cent. Creatinine clearance: 52 c.c. of plasma cleared per minute; creatinine: 1.7. The patient was discharged on the twenty-sixth hospital day.

Follow-up. On Feb. 1, 1961, office examination showed the vulva to be normal; there was no evidence of enlargement of the Bartholin gland on the left. Skin graft 99 per cent take; blood pressure was 140/70. Evaluation of renal function planned in 3 months, 6 months, and 12 months.

Comment

One such experience is enough to alert and remind us of the possibility that an apparently ordinary infection may, without prodromal warnings, erupt into critical, really life-threatening illness. Adams and Pritchard's[1] more recent and comprehensive report has emphasized the possibility of a similarly acute problem developing during the management of infections in either pregnant or nonpregnant patients. As a result of their experience, they have suggested that all febrile patients should be watched closely to detect the onset of hypotension. They have also emphasized that a drop in body temperature may precede the drop in blood pressure and may well serve as a warning that the sequelae of hypotension can be anticipated.

When infection complicates abortion, not all of the more malignant infections are due to gram-negative organisms. Deaths resulting from abortion continue to be reported after *Clostridium welchii* has accounted for high fever, vomiting, diarrhea, and rapid hemolysis before terminal renal failure. Saprophytic strains of encapsulated gram-positive bacilli of the Clostridium group may account for dramatically rapid deaths due to "gas gangrene." Only occasionally complicating abortion, and then usually evident clinically, the cases of gas gangrene seem more likely to develop when premature separation of the membranes, retention of a dead fetus, or a traumatic delivery result in the presence of devitalized tissues within a contaminated vagina and uterus. In *Cl. welchii* infections, it is the massive hemolysis which burdens the renal cortex and results in anuria and the probability of acute renal necrosis.

On the other hand, it is the hypotension developing during bacterial or septic shock which at first results in anuria, but oliguria is likely to persist after normal blood pressure has been restored because of the severe renal necrosis which has developed during the stage of hypotension. In some instances this renal damage may be speeded by intravascular clotting, miliary thrombi, and infarction within glomeruli as well as cortical parenchyma. McKay, Jewett, and Reid[8] have emphasized the probable role of such emboli in the pathogenesis of cases developing foci of renal, intestinal, pituitary, or adrenocortical necrosis. Studdiford and Douglas[9] were particularly impressed by the difficulties within the pulmonary circulation and by the persistence of cyanosis and pulmonary edema even after peripheral resistance and intravascular tension had been restored. The differential diagnosis may at times rest between bacterial shock and the hemolysis and anuria incident to *Cl. welchii* infection. In the patient exhibiting bacterial shock, the hypotension is usually sudden in onset and likely to prove unyielding to all ordinary therapy. The *Cl. welchii* case may also exhibit shock and pulmonary edema, but there is usually a high fever, more marked leukocytosis and the characteristic evidences of gas production within the tissues. With bacterial shock, the white count is significantly unchanged and has often been within normal limits at the onset of the severe hypotension.

The importance of an accurate diagnosis, since it usually initiates prompt and essential treatment, is again evident in the recent case report by Barret, Eadie, and Mandell.[3] They have summarized the course of a fatal illness due to bacterial shock in the last trimester of pregnancy to emphasize that the patient's failure to respond to blood transfusion and pressor agents other than norepinephrine might well and promptly suggest bacteremia and endotoxic shock rather than the hypotension incident to blood loss. To appreciate the pathogenesis toward which

treatment must be directed, Adams and Pritchard[1] have likened this sequence to the Shwartzman reaction, as had been emphasized by McKay, Jewett, and Reid.[8]

When infection complicates abortion, the possibilities of placental bacteremia probably depend upon the presence of a large focus of bacteria within somewhat isolated tissues not readily entered by or affected by the antibiotics given to the mother. It would be well to remember also, that the bacterial foci accountable for the escape of virulent toxins may lie within the fetal circulation and thus be confined to the uterus. Usually no other sites of infection have been found at autopsy in the fatal cases. Such isolation is particularly evident when fetal death occurs and circulation within the fetal vessels stops. Studdiford and Douglas[9] have reminded us that the placental membrane represents an area exposed to maternal circulation of approximately 7 sq.m. at term, through which enormous area for diffusion the products of bacterial growth and tissue decomposition may enter the maternal circulation in overwhelming quantities.

From the standpoint of preventing the development of septic shock during the progress of an abortion, it would seem, therefore, that effective treatment must include prompt and complete removal of the probable sources of bacterial proliferation and toxin formation. While such débridement occurs spontaneously in most cases of infected abortion, when indicated, prompt and adequate curettage and occasionally hysterectomy may be lifesaving. Studdiford and Douglas have emphasized that removal of the placenta and uterus, if such an operation is to be effective, must be carried out within 12 hours after the onset of hypotension.

Among the nonpregnant, the effectiveness of removing an infected uterus and adnexa, in spite of the almost terminal appearance of the gynecologic patient with large ruptured tuboovarian abscesses, must be due to the benefit of a débridement of massive foci of the bacteria that were beginning to shower the general circulation with shock-producing endotoxins. In the light of increasing knowledge concerning the mechanisms of such bacterial shock, what may once have appeared to be a heroic operation in such cases becomes not only justified but obviously essential.

Grove[4] has discussed the more frequently evident errors in the treatment of septic or bacterial shock. Regarding the patient's warm skin, flushed appearance, rapidly bounding pulse, and fever as evidence of satisfactory "resistance" to severe infection is a danger to be emphasized. Only by frequent use of the sphygmomanometer can the usually precipitous drop in blood pressure be detected early enough to institute effective treatment and thereby minimize the inevitable renal damage. Altemeier and Cole[2] noted the development of bacterial shock during the course of diffuse peritonitis or with the development of large abscesses. The case we are reporting herein illustrates the possibility of a comparatively minor lesion resulting in an equally disastrous state of shock.

The literature indicates recognition of this syndrome as early as 1831, when Grove stated it was first described by Laennec, but effective means of treatment have become available only in very recent years. It is most essential, however, that we be on the alert for these cases, for these patients now can be saved. Grove believes it is a grave error not to follow a thorough plan of management and outlines the measures he believes should be included. Adams and Pritchard[1] have emphasized follow-up observations indicating that if the patient survives organ function can be expected to return to normal. We can no longer justify failure to recognize this entity, just as we cannot fail to meet the occasional challenge that requires far more than routine treatment.

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Hysterocolpectomy for the treatment of uterine procidentia

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HYSTEROCOLPECTOMY, that is vaginal hysterectomy with total vaginectomy, is one of many surgical procedures used for the correction of genital prolapse. When one speaks of the proper treatment for genital prolapse one must define the circumstances present. It is an accepted gynecologic precept that no one surgical procedure is ideal for the correction of all such cases. The type of operation selected will be governed by multiple factors, such as the presence and degree of cystocele, rectocele, and enterocele, the degree of uterine prolapse, the presence of adnexal or uterine pathologic conditions, and the associated symptoms. Also to be considered are the age of the patient and the need or desire on her part to preserve menstruation, reproduction, and a functional vagina. When these multiple factors are evaluated with respect to a particular case, one of the conventional procedures will suggest itself as the operation of choice. Among the ever-increasing number of geriatric patients are those with genital prolapse who no longer need or wish to preserve a functional vagina. The term "geriatric" will in many cases be synonymous with a poor operative risk and a debilitated patient. It is these patients for whom the combined procedure of vaginal hysterectomy and total colpectomy will have much to offer.

Although most commonly prolapse appears after the childbearing age, it may appear from the mid-twenties throughout life. It is a gradual process and may be tolerated for many years. Some patients will stoically accept the inconveniences of such a condition for 15 to 20 years, and only when it becomes a debilitating disease and a family nuisance will they submit to surgical treatment. In other patients this condition will not appear until very late in life. In either case, we are then presented with procidentia in an elderly patient. A few decades ago, the normal attrition of life would have claimed many of these patients before the procidentia had become a problem, or even appeared.

Inversion of the vagina or prolapse of the cervical stump following previous pelvic operation is another facet of the same problem. This is a most distressing and incapacitating condition. These debilitated and unhappy people are in great need of a satisfactory and dependable operative procedure. Adams[1] pointed out this need for a procedure that would relieve the symptoms completely and give good permanent support without fear of recurrence. Once again, if the need for a vagina no longer exists, a hysterocolpectomy, or total colpectomy, will meet all these requirements.

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Similar procedures

There are few subjects in gynecology that have produced such a voluminous literature as that available on the treatment of prolapse or procidentia. However, there are only a few papers on hystercolpectomy or total vaginectomy. According to Rubovits and Litt,[2] colpocleisis was first performed by Gerardin in 1823 and by Neugebauer in 1867. Isolated cases were also reported in 1898 by Baldy[3] and Beyea.[4] The majority of these early operations were done because of an irreducible and strangulated uterine prolapse.

The first modern colpocleisis was developed by Dujarier and Larget[5] in 1920. This operation consisted of total vaginectomy with amputation of the cervix. The cervical stump was sutured tightly and the fundus left in place. The vaginal cavity was obliterated by approximating the levator ani muscles and suturing the bladder and rectum together. Phaneuf,[6] in 1935, reported 5 cases managed by this same technique—amputating the cervix, leaving the fundus, and obliterating the vagina by suturing the rectum and bladder together.

Williams,[7] in 1950, added two refinements, first, by performing a vaginal hysterectomy and, second, by suturing the pubococcygeus muscles together in the midline. In 60 successfully treated patients, he emphasized the importance of uniting the pubococcygeus muscles. Adams,[1] a year later, reported a series of 30 cases of vaginal prolapse, mostly after hysterectomy, treated successfully with total colpectomy. In 1958, Cox[8] reported his series of 147 cases of hysterocolpectomy for uterine procidentia using an entirely different technique.

These three series of cases mark the transition in the use of hysterocolpectomy from a procedure of last resort to one of primary choice, under the proper circumstances. Up to this time the majority of corrective measures for procidentia have been designed to reconstruct and preserve the vagina, while hysterocolpectomy or total colpectomy has been reserved for the final solution of many previous operative failures. Even in the best of hands, a satisfactory operative result with preservation of the vagina may not remain so and may not always achieve a satisfactorily functioning vagina. The operation to insure against a recurrence of the prolapse may have to close the vagina so snugly, or so foreshorten it, that sexual relations are impossible. Symmonds,[9] reporting a series of cases operated upon for prolapse, preserved the vagina in 34. In 13 of these patients, the vagina was not maritally satisfactory.

Advantages and disadvantages

It is our belief that hysterocolpectomy should be strongly considered as a corrective procedure of choice for genital prolapse in an elderly patient if she no longer wishes to retain the vagina. In the main, these patients have poor tissues that are markedly atrophied and attenuated and are not good for difficult and highly technical procedures. This operation is easily done with a much shorter operating time than other procedures. The complications are few and the results are good.

The indications for this operation are quite simple: (1) uterine procidentia or prolapse in the patient for whom the vaginal canal no longer serves a useful purpose; (2) procidentia in elderly, poor-risk patients; (3) inversion of the vagina after previous pelvic operation.

The contraindications are equally simple: This is not a good operation for the younger patient to whom the vagina is most important.

The standard technique of hysterocolpectomy has been to obliterate the vagina by suturing the bladder to the rectum. The literature is not specific as to the postoperative comfort of these patients. It seems inescapable that this would result in bladder pull and discomfort and perhaps some disturbance in the mechanics of voiding. The pubococcygeus muscles are approximated and the levator muscles are sutured together in the midline. There again, no mention is made as to whether or not the resultant rigidity of these tissues produced discomfort. Symmonds[9] reported a bilateral hernia into

the ischiorectal fossa following suturing the levator muscles in this manner.

Operative technique

Because of our dissatisfaction with mechanical devises and with the results of other operative procedures, we first performed a hysterocolpectomy according to the Cox[8] technique some 5 years ago. This operation differs from all other procedures in several ways. The most important difference is that the bladder and rectum are returned to their normal anatomical positions in the pelvis. This relationship is maintained by means of iodoform gauze packing. We have not established surgically any abnormal relationships.

The operative technique of hysterocolpectomy is not difficult. There are several steps in the procedure which, if observed, will facilitate the operation, cut down the blood loss, and sponsor more rapid healing.

A vaginal hysterectomy is first performed. This may be done by any technique favored by the operator. We feel it important to circumcise the cervix at the cervicovesical junction and to remove the uterus through the exposed area thus provided. If the anterior vaginal wall is opened prior to removal of the uterus, a needless blood loss will occur. Often the tissues are so atrophied that one clamp will include the entire broad ligament with its contents and appendages. After the uterus is removed the peritoneal cavity is closed and the cardinal ligaments are sutured together in the midline.

For the vaginectomy, a circumvaginal incision is made just within the hymenal ring. It should be emphasized that this incision should not be more than 1 to 2 mm. within the ring. If a greater vaginal cuff is left, epithelization proceeds more slowly and the end result is less perfect. Anteriorly, this incision passes about 0.5 cm. below the urethral meatus.

The anterior vaginal wall is then dissected free from the bladder and urethra and incised in the midline to the circumvaginal incision. The posterior vaginal wall is grasped at the fourchette and freed from the rectum throughout its extent to the vaginal vault. The posterior vaginal wall is incised in the midline.

Each half of the vaginal cuff is then excised. The dissection is best begun at the circumvaginal incision and carried toward the vault by sharp and blunt dissection. There are usually several small vessels at 3 and 9 o'clock which require ligation.

At this point we deviate from previous operative procedures in that we do not obliterate the vagina with the massive suture technique. Instead, the bladder, rectum, and vault of the vaginal cavity are returned to their normal position and relationship within the pelvis. The cavity is then tightly packed with 2-inch iodoform gauze and a Foley catheter placed in the bladder. If the introitus is gaping, a good perineorrhaphy will tighten it up and narrow the orifice. This may be necessary to secure tightly fitting packing.

Postoperative course

The postoperative care is mostly routine. There is a moderate amount of serous drainage for 36 to 48 hours, which gradually becomes less in amount. Routine perineal care and irrigation of the catheter is all that is needed. These patients are generally interested in solid food the next day.

On the eighth postoperative day the catheter and packing are removed. The vaginal cavity has now contracted down to a small rigid tube. Granulation tissue has formed all around the vagina. With the packing out there is no need to fear a recurrence—everything is supported and fixed in its proper place and will not slide out. In about 3 or 4 weeks the entire cavity will have granulated in and the surface will have become completely epithelized. The end result will be a smooth, symptom-free dimple.

Personal experience

In the past 5 years we have performed this operation on 11 patients. Ten of these had procidentia and one had inversion of the vagina following a previous hysterectomy.

These patients had had symptoms for from 2 months up to 18 years. The oldest patient was 80 years and the youngest 55 (whose husband was impotent), with an average age of 68.1 years. It is of interest that the average age of onset of symptoms was 60.3 years. Six of these patients were married, 4 were widows, and 1 was single.

Postoperative complications were, in the main, a continuation of the preoperative medical conditions. To illustrate, these patients had the following diseases: facial neuralgia, chronic spastic colitis, obesity, hypertension, hypertensive cardiovascular disease, myocarditis, congestive heart failure, left ventricular hypertrophy, epilepsy, diabetes mellitus, degenerative arthritis, and osteoarthritis. Two patients developed postoperative phlebothrombosis which responded to medical management with anticoagulants. There was one case of postoperative segmental atelectasis which cleared up in a few days.

The average hospital stay was 15 days, and there were no deaths. Ten of these patients were re-examined in the past month. They were completely relieved of the pain and pressure symptoms, were free of recurrence, and enjoyed good support. Eight of the 11 patients had marked urinary symptoms prior to operation with frequency, nocturia, and incontinence. Some required manual compression to void. Two of these patients still have moderate nocturia. One patient has mild stress incontinence and one patient has chronic urethritis with a stricture that is being treated by a urologist. This was also a preoperative problem.

The advantages of this operation over other operative procedures are many. In the geriatric patient this is a relatively safe and easy operative procedure which will cure a difficult situation. It has even been performed on bedridden patients and solved a messy nursing problem. The results are good and the patient can anticipate relief of symptoms with a comfortable support. There is no need to fear a recurrence as the cure will be permanent.

The single disadvantage is the complete and permanent obliteration of the vagina with the loss of all marital functions. Actually this has not proved to be a point in these patients. In most of them, due to their age, the loss of the vagina was not important. In the younger patient the prolapse had been so longstanding, debilitating, and confining that a complete cure was a welcome solution. Not one patient has complained because of the loss of the vagina.

Comment

Geriatric problems are rapidly mounting. Genital prolapse is a problem that will, with increasing frequency, be brought to the gynecologist by the very aged patient. When surgical correction of the prolapse is contemplated and when a functional vagina is no longer desired by the patient, hysterocolpectomy should be among the considered procedures.

The concepts of the technique described differ basically from those previously described and, we feel, will produce a more normal physiologic result.

Summary

The indications and steps in the technique of hysterocolpectomy for procidentia are described.

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Discussion

Dr. H. Fleming Fuller, Kinston, North Carolina. Hysterectomy with some method of obliteration of the vagina is an excellent procedure when indicated. I would hesitate to perform the operation on a 55-year-old woman, even though her husband was impotent, for she could possibly remarry.

I agree with the essayist in his technique of not opening the anterior vaginal wall before removing the uterus, thus preventing a needless blood loss. Is there any effort made to support bladder and rectum by plicating the pubocervical fascia and fascia propia prior to inserting the vaginal pack?

Dr. Thompson leaves the pack and catheter in for 8 days. He mentions the presence of a moderate amount of serous drainage for 36 to 48 hours. One cannot help but compare this operation with the clamp hysterectomy with pack made famous by Dr. Joseph Price and recall Dr. Archibald Campbell's statement "There is no operative procedure in pelvic surgery which gives such abundant drainage as that exhibited by the clamp method of removing the uterus."

Hysterectomy and obliteration of the vagina is preferable to the old LeFort procedure of leaving in the uterus. My preference, however, is vaginal hysterectomy with anterior and posterior repair and colpocleisis. In this procedure the operative site is allowed to heal by primary healing rather than secondarily as described in the hysterocolpectomy, where healing takes place by granulation. We remove the uterus in more or less conventional manner. The uterosacral ligaments are approximated with 4 to 5 interrupted plicating sutures, the posterior half of the peritoneum gathered in each suture. The anterior and posterior peritoneal surfaces are closed and the cut ends of the round and uterosacral ligaments are tied together over this closure. The reflected pubocervical fascia is approximated snugly or imbricated to support the bladder. The vaginal mucosa is removed out to the hymenal ring. A generous perineorrhaphy is then done. The vaginal mucosa is closed longitudinally, care being taken not to approximate the anterior and posterior mucosa too close to the introitus. In this manner distortion of the urethra is prevented, thus alleviating the possibility of postoperative stress incontinence. The postoperative care for these patients is the same as that for the routine vaginal hysterectomy. So far, our end results have been good.

Dr. John H. Ridley, Atlanta, Georgia. A 10 year survey of the colpocleisis procedures, of various techniques by various operators at the Grady Memorial Hospital of Atlanta from 1946 through 1956, revealed that 20 had been performed. Postoperative evaluation brought out two interesting facts!

First, 9 patients had either induced or uncorrected urinary stress incontinence. This varied from mild in 5 patients to moderate in the remainder. This condition might be expected because of the altered urethrovesical angle, as the base of the bladder is brought downward, fixed, and thus straightened.

Second, 8 patients had a varying amount of prolapse of the urethral mucosa giving some trouble because of pain or actual ulceration.

Final evaluation by direct questioning of the patients, however, failed to reveal a single patient who was not satisfied and willing to tolerate the above-mentioned inconveniences for the relief obtained.

Let me question the advantage of packing the denuded vagina rather than obliterating it at the time of operation. By obliteration, the patient may be ambulatory on the second or third postoperative day with catheter removed. This is important in the aged individual to prevent phlebothrombosis, atelectasis, and bladder complications from the indwelling catheter. Then there is the period of "about 3 or 4 weeks" during which time healing by granulation takes place. Does the patient have a troublesome discharge and bleeding during this time? Is there much local pain during this time of healing?

Most gynecologists agree that hysterectomy is desirable in the aged individual with prolapse but there is the impression also that if no evidence of malignancy is found before or during operation that the simple colpocleisis of LeFort offers less surgical risk in certain patients.

Dr. Robert Barter, Washington, D. C. Dr. Thompson says that his patients stayed in the hospital an *average* of 15 days following this procedure. I would want to know what was the longest stay in the hospital following the procedure.

Phlebothrombosis or thrombophlebitis in 2 of the 11 patients is a rather high percentage for that complication, particularly when many of us feel that one of the many advantages of vaginal hysterectomy is the fact that there are

fewer vascular complications postoperatively than there are following abdominal hysterectomy.

The statement with which I disagree most heartily, however, is that this operation can be done "better" in the so-called poor surgical risk patients. I think that vaginal hysterectomy and a repair can be done just as expeditiously and, as far as I am concerned, much better than the operation under discussion.

I have never agreed with the technique of filling the vagina with surgical dressing or a pack. Certainly one of the reasons why these patients do heal ultimately is that they heal by secondary intention. I'm sure that all such patients become infected by having a pack left in the vagina for such a long time.

DR. THOMPSON (Closing). It has been asked whether there is any objection to plicating the bladder during this operation, particularly in patients with stress incontinence. There is none whatever and we have done this on occasion.

Dr. Ridley mentioned 9 patients with urinary stress incontinence. In the past month we have interviewed 10 of our 11 patients and only one of them has a residual mild stress incontinence. This patient felt that this was a small price to pay for the complete relief she has received.

In reply to Dr. Barter, inasmuch as I do not have the figures with me, I cannot tell you the longest stay in the hospital of any of these patients. This was, without doubt, one with phlebothrombosis as a complication.

Response of fibromyomas to a progestin*

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NORETHYNODREL is one of a group of new oral progestins in the 19-nortestosterone group. It is a potent oral progestational agent and has the ability to inhibit the pituitary gland. Norethynodrel is combined with 1½ per cent of ethinylestradiol 3-methyl ether. This latter substance was originally reported to have a weak estrogenic potency at about the same level of activity as estrone.[5, 7] More recent research data utilizing the Ruben test have shown that it is as active orally as estrone is when given parenterally.[34] Other tests suggest that it is even more active than the above experiment indicated. In addition to the added estrogenic substance, norethynodrel has mild inherent estrogenic activity of its own.[7] (The combination of 98½ per cent norethynodrel and 1½ per cent ethinylestradiol 3-methyl ether will be referred to simply as norethynodrel hereafter.)

Norethynodrel has been proposed for use in dysfunctional uterine bleeding,[1, 2, 4, 13, 28, 30] amenorrhea,[22] habitual abortion,[6, 11, 24, 32] threatened abortion,[13, 14] endometriosis,[2, 3, 10, 15] dysmenorrhea,[4, 29, 30] premenstrual tension,[30] infertility due to inadequate luteal phase,[4, 32] delay of menses for convenience,[9] and oral contraception.[1, 23, 32]

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**Norethynodrel with ethinylestradiol 3-methyl ether furnished as Enovid by G. D. Searle & Company, Chicago, Illinois.*

This report is based on the observation that norethynodrel causes an increase in the size of fibromyomas of the uterus.

When norethynodrel was first made available to the Gynecologic Endocrine Clinic at the Jackson Memorial Hospital, it was used in many conditions, including endometriosis. Because endometriosis is so uncommon in this clinic, the drug was made available to a few private patients. The first case (Table I, Case 3) was that of a private patient of a colleague who instituted norethynodrel for the pseudopregnancy treatment of endometriosis. The patient was a 31-year-old nulliparous woman with primary infertility and pelvic pain. The fundus of the uterus was irregular and slightly enlarged. After 2½ months of amenorrhea, the uterus was the size of an 11 weeks' gestation. One and one-half months later, the uterus was firm, irregular, the size of a 14 weeks' gestation and was felt three fourths of the way to the umbilicus. She was subjected to panhysterectomy because of the rapidly enlarging tumor mass. At operation, the uterus was enlarged as described, because of multiple large fibromyomas which did not appear remarkable otherwise. Histologic sections confirmed the diagnosis but were not remarkable.

The second case (Table I, Case 7) was in a 35-year-old nulliparous patient with primary infertility whose problem was small fibromyomas and menorrhagia. She refused myomectomy or hysterectomy. Since this occurred early in our experience with norethynodrel, it was elected to attempt complete suppression of menses, which would control blood loss and at the same time give information regarding the minimum

dose necessary to maintain amenorrhea. There was rapid and marked enlargement of the tumor mass to the size of a 14 to 16 weeks' gestation and in 2 months the patient was told an operation must be performed because of the possibility of cancer. She continued to refuse operation, the treatment was stopped, and the tumors returned to the pretreatment size. It was then that the effect of norethynodrel on fibromyomas was realized and this study was begun.

Materials and methods

Sixteen patients who had fibromyomas of the uterus received norethynodrel in sufficient dosage to maintain amenorrhea. Three were private patients who received the drug for endometriosis, and fibromyomas were an incidental finding. Thirteen were clinic patients who had small fibromyomas and received norethynodrel in order to observe its effect on the tumor growth. This could be justified because the patients also had menorrhagia and a period of amenorrhea permitted better replacement of the blood volume and hemoglobin mass by diet and iron therapy.

The range of age was 29 to 48 years and parity ranged from 0 to 6. The treatment was continued for a period of 4 to 24 weeks but almost all for at least 7 to 8 weeks. Two patients received two separate courses of treatment (Table I, Cases 5 and 8). The dose was the amount sufficient to maintain amenorrhea and varied from 20 to 40 mg. daily but most often 30 mg. daily.

It has not been possible to measure the size of fibromyomas objectively and no means of accomplishing this has been devised for this study. Considerable subjective error is recognized in determining size by the usual means of pelvic examination, sounding the endometrial cavity, and measuring the height of the fundus. An attempt was made to diminish this error by submitting the patient to examination by two attending physicians and one resident physician at each visit. Visits were made every 2 weeks and the examination was done and recorded without knowing the previous findings, dose of the drug, or at what stage in the study the examination was done.

There was follow-up in all but 4 cases for determination of the size after treatment

Table I. Response of fibromyomas to norethynodrel*

Case	*Pretreatment size*	*Treatment period*	*Maximum size*	*Follow-up period*	*Posttreatment size*
1	Normal with 4 cm. nodule	8 weeks	18	11 weeks	10
2	Normal with 2 cm. nodule	8 weeks	12 with 5 and 2 cm. nodule	6 months (only examination)	12 with 1 cm. nodule
3	6	16 weeks	14+	Hysterectomy	Hysterectomy
4	Normal	20 weeks	12	11 months	Normal
5 a.	6	6 weeks	14	4 weeks	6
b.	6	14 weeks	16	6 weeks	8
6	6	5 weeks	12	8 weeks	12
7	8	6 weeks	14	5 weeks	8
8 a.	10	4 weeks	14	4 weeks	8
b.	8	8 weeks	14	4 weeks	10
9	10	7 weeks	14+	8 weeks	10
10	10	10 weeks	14	5 weeks	6
11	10	11 weeks	14	None	Lost
12	Normal	6 weeks	10	8 weeks	6
13	Normal	10 weeks	Normal with 3 cm. nodule	None	Lost
14	8 with 2 cm. nodule	5 weeks	8 with 4 by 4 cm. nodule	12 weeks	8 with nodule not felt
15	5 cm. nodule	4 weeks	7 cm. nodule	None	Lost
16	9	6 months	9	1 and 5 months	9

*Measurements of size are in weeks' gestation.

was withdrawn. One case ended by hysterectomy and 3 were unavailable for further study. The posttreatment examinations were made 4, 8, and 12 weeks after treatment.

The findings were described in a range of 2 weeks' gestation, such as 8 to 10 weeks or 10 to 12 weeks, with the size thought to be most close to the size of the uterus underlined. The total tumor mass plus uterus was interpolated into the term "weeks' gestation" and this too presented difficulties in trying to interpret grossly irregular tumors. Occasionally descriptions of individual myomas were included where it seemed to emphasize the result.

The size has been narrowed to the single most consistent finding in order to simplify the accompanying table. This simplification does not alter the accuracy of the results when compared with the over-all picture as seen on the patient's records. When the size is described as normal, this indicates that the total mass is within the range of normal variation in size but irregularity of fibromyomas were noted before treatment was begun.

Results

Fifteen of 16 patients treated showed significant enlargement of the fibromyomas. The initial size, treatment period, largest size, follow-up period, and posttreatment size are indicated in Table I. The follow-up period may represent the only examination obtainable or the length of time before the size reached its smallest dimensions after treatment was discontinued. The cases are numbered in the order of decreasing degree of response.

In 9 instances (one case on two occasions) there was dramatic enlargement, sufficient to be startling and disturbing. In 8 instances the enlargement was definite but not marked.

Most often the maximum size was reached in 4 to 8 weeks and then it began to stabilize. However, except for 3 patients with endometriosis, the amenorrhea was not continued longer than 12 weeks and what would happen to these tumors on very prolonged therapy is not known.

In 10 instances, the tumor reduced significantly in size after treatment, returning to the pretreatment size, nearly the same, or smaller. Two of these instances represent the second as well as the first course of treatment in 2 patients.

In 3 cases, significant enlargement persisted after treatment was stopped. This represents 3 out of 11 of those patients followed in whom the fibromyomas remained significantly enlarged after treatment was stopped.

It is recognized that the natural course of fibromyomas is one of unpredictable growth —unpredictable as to the rate of growth, when the growth will occur, and what the ultimate maximum size will be. It may be that the significant enlargement which persisted after treatment was stopped represented normal growth of the tumor.

There was some decrease in the size of the tumors in all cases which were adequately followed after treatment was stopped and there was return to pretreatment size in 70 per cent. From this it must be concluded that the major activity causing increased size of the tumors was a result of norethynodrel stimulation and not due solely to natural growth. That there is considerable variation in the degree of response or responsiveness is apparent from Table I which indicates the differences in the change in size.

In only one case was there no enlargement (Case 16). The patient was under treatment for endometriosis with amenorrhea for 24 weeks resulting in marked improvement. She was subjected to hysterectomy 5 months later because of profuse menorrhagia. The presence of a large single pedunculated submucous fibromyoma was then discovered and what had happened to the tumor size during treatment with norethynodrel is not known but the uterus had not enlarged.

Operation in 2 cases, months after treatment, confirmed the presence of fibromyomas. Unsuspected endometriosis and a minor degree of adenomyosis was also noted. The first patient treated and previously

mentioned was the only one subjected to operation while on therapy.

Comment

There is much to be learned about this relationship between norethynodrel and the increased size of fibromyomas. We select the term "increased size" rather than "growth" because we do not know what element or elements are responsible for the change. Edema, vascular congestion, increased collagen or increased muscle tissue may be factors singly or collectively. Although there is much we do not know and this report is preliminary, there is one thing that is certain. Norethynodrel causes significant and many times a rapid and marked increase in the size of fibromyomas during an amenorrhea-producing use of the drug.

Seven cases of enlargement of fibromyomas were reported by Mixson[21] in a report on norethynodrel therapy. Andrews and coworkers[2] reported 7 cases. They noted marked speed and degree of enlargement of fibromyomas in the 7 patients while under treatment for endometriosis with return to pretreatment size after treatment was withdrawn.

Lebherz and Fobes[16] reported 92 cases of endometriosis treated with norethynodrel.[16] Among these were 4 patients with fibroids and in all 4 cases there was rapid and dramatic growth of the fibroids. Hysterectomy was resorted to in 2 cases because of associated severe pain. Both patients operated upon had fibromyomas with red degeneration.

In spite of the extensive recent literature on norethynodrel, these are the only reports referring to this phenomenon. The use of the drug for the conservative medical control of endometriosis is becoming increasingly widespread. The problem becomes grave when young women who deserve and are receiving conservative treatment are subjected to a hysterectomy because this phenomenon is not known. The fact that norethynodrel causes increase in the size of fibromyomas needs emphasis.

Although we have not conducted studies on the effect of intermittent use of norethynodrel on fibromyomas, this should be done. Norethynodrel has been approved by the Food and Drug Administration as an oral contraceptive and is already widely used for this purpose. Because the effect is so rapid and marked, it is reasonable to suspect that fibromyomas may enlarge significantly on the dosage proposed for contraception.

Another aspect of the relationship of norethynodrel to fibromyomas is that for the first time a drug is reported which does cause a significant increase in the tumor size.

A review of the literature indicates that estrogen is most commonly thought to be the source of stimulation of fibroid growth, but the reports and research to confirm this are not very convincing. Certainly, the natural course of the disease of fibromyomas indicates hormonal influence. Witherspoon[33] is usually quoted in support of the estrogen theory. He reported a group of 44 patients who had endometrial hyperplasia and no demonstrable evidence of fibromyomas. An average of 4 years, 9 months later, each of the 44 patients had hysterectomy because of fibromyomas of the uterus. In 40 of the cases, the endometrium showed hyperplasia at the time of hysterectomy. Witherspoon postulated that unopposed estrogen over a long period of time was the factor igniting fibroid growth. Timonen and Vaananen[31] performed bioassay studies of patients with fibromyomas and reported essentially normal levels for 17-ketosteroids, FSH, and pregnanediol, but elevated estrogen levels.

Two reports stand out against the growth stimulation effect of estrogen. Hurxthal and Smith[12] included 5 patients with fibromyomas in a group of patients with endometriosis who were receiving pseudopregnancy treatment with stilbestrol and they did not report any increase in the size of the tumors. Karnaky,[14] who was the first to use prolonged stilbestrol treatment for endometriosis, reports that he has observed fibromyomas decrease in size and sometimes dramatically decrease while the patient was taking stilbestrol. Both investigators use the synthetic estrogen, stilbestrol.

Seitchik[27] proposes an interesting theory on the mechanism by which stilbestrol is effective in endometriosis. This theory depends upon the fact that estradiol-17-beta is the natural estrogen necessary for normal endometrial activity. Stilbestrol acts by inhibiting FSH which in turn decreases the amount of estradiol-17-beta. Stilbestrol also inhibits the local action of estradiol-17-beta in the oxidative metabolism of the endometrium. When applied to fibroids, this may explain why the tumors do not increase in size on stilbestrol and may regress. They may be dependent upon estradiol and this is blocked during stilbestrol therapy. The estradiol present in norethynodrel, therefore, may be a factor in tumor growth. No experiment has been found reported in the literature where estradiol is given to patients with fibromyomas for a prolonged period.

It has not been possible to reproduce true fibromyomas in experimental animals and the work reported using estrogen in experimental animals deals with fibromas. It does not seem practicable to try to apply this work to the human fibromyoma.[17, 18]

Goodman[8] reported 7 cases of patients with fibromyomas treated with progesterone in which there was a decrease in the size of the uterus in all as determined by bimanual pelvic examination. On the other hand, Segaloff and associates[26] administered progesterone to women with fibromyomas for 30 to 109 days and observed no decrease in size by hysterogram and no increased involution microscopically. He did suggest evidence of increased cellular activity microscopically, but did not describe any increase in the size of the fibromyomas.

In a recent article reporting unsuccessful attempts at tissue culture of fibromyomas, Miller and Ludovici[20] emphasized the very limited amount of experimental work which has been conducted into the study of fibromyomas. In a review of the literature on etiology and histogenesis of fibromyomas, Leon[19] also emphasizes the paucity of research work and basic understanding of fibromyomas.

Previously only pregnancy was known to cause an increase in the size of fibromyomas. Randall and Odell[25] even attempt to cast doubt on this and concluded that apparent enlargement of myomas during pregnancy was probably not because of actual growth. The method of study in their experiment was very limited and depended principally on the microscopic appearance when routine staining techniques were used. More elaborate methods available today might reverse their conclusion. By the use of norethynodrel as well as pregnancy, studies can be conducted on fibromyomas in the course of increasing size or involution with use of special stains, enzyme studies, etc.

Summary

Norethynodrel has been shown to cause significant increase in the size of fibromyomas in 15 of 16 cases during amenorrhea-producing use of the drug. In about half of these, the enlargement was rapid and marked in degree. In most but not all the tumors decreased to about the pretreatment size following cessation of therapy. Three remained enlarged.

It is important that this phenomenon be understood by all who are using norethynodrel as a conservative means of treating endometriosis so that unnecessary hysterectomies will not be done. Until more information is available, routine follow-up pelvic examinations should be done on patients who receive this drug as a contraceptive, particularly if they are noted to have fibromyomas.

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Discussion

Dr. Mason C. Andrews, Norfolk, Virginia. During pregnancy, the tendency of myomas to enlarge significantly is well known. It would be surprising if any exogenous hormones which produce other tissue responses characteristic of pregnancy did not also produce this one.

We have twice had the opportunity to observe microscopic myomas enlarged by pseudopregnancy, and, as during pregnancy, hypertrophy of the individual cells appears to be responsible. There is clearer cytoplasm, suggesting increased glycogen. This process would be expected to be reversible and Dr. Mixson's experience as well as ours would suggest that myomas usually return to their previous size after withdrawal of the responsible hormones.

The question must be raised as to whether the natural growth of a myoma would be accelerated by an induced pseudopregnancy and this tendency constitutes, therefore, a contraindication to this treatment in patients having myomas. Since some growth of some myomas must be expected in the absence of any medication, I would interpret available evidence as being reassuring, since the incidence and degree of persistant growth appears to be relatively small after pseudopregnancy and even possibly coincidental.

Another question raised by this paper is whether estrogen and progesterone in doses equivalent to 5 to 10 mg. of norethynodrel given for 20 days beginning on the fifth day of a cycle may accelerate myoma growth. My brother and I have used this dosage in well over 100 patients including many with myomas and can demonstrate no such effect. These patients have been under treatment for menorrhagia and dysmenorrhea or have used the drug for contraceptive purposes.

The gross and microscopic appearance of the endometrium which has been stimulated from the fifth to the twenty-fifth day with this drug is most inactive in both the epithelial and stromal elements, much less active in fact than during a normal cycle. I would expect that the myometrium and myomas would be no more stimulated than during a normal cycle and probably would be less so.

Dr. Robert Greenblatt, Augusta, Georgia. First, certain terms need to be defined. Pseudopregnancy must not be used in the same sense that it was employed by the essayist. Giving large doses of an estrogen may suppress menstruation for long periods of time, but that is not pseudopregnancy. Estrogens alone do not

imitate the hormonal picture of pregnancy as does the administration of estrogen and progesterone. By the administration of slowly increasing doses of a potent estrogen-progesterone compound, menstruation may be suppressed for nine months' time, hence the term "pseudopregnancy."

Second, I want to correct another misconception. When norethynodrel is employed, one should realize that every 10 mg. tablet contains 9.85 mg. of norethynodrel, a very potent progestational agent, and 0.15 mg. of the 3-methyl ether of ethinylestradiol. Furthermore, it should be emphasized that this estrogen is about twenty-five times more potent, milligram for milligram, than estrone. It is by far the most potent estrogen available today, ten times more potent than stilbestrol, and twenty-five times more potent than estrone. If there is a factor responsible for the increase in size of fibromyomas, it may be the overriding effect of this powerful estrogen when norethynodrel is employed. Progesterone has been shown to be antifibromatogenic in the guinea pig, but progesterone has not proved of any value in the clinical management of uterine fibromyomas. I am not surprised if norethynodrel does stimulate the growth of fibromyomas, for in pregnancy this is often the case.

Palliation in gynecologic cancer

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IT IS well documented that many women with pelvic malignancy are not curable by any method now known. It is apparent, therefore, that considerable time and effort must be devoted by the gynecologist, the radiologist, and the neurosurgeon in their efforts either to prolong life or, more important, to make the remaining days of these patients' lives more comfortable and productive. The following presentation is an effort to summarize the experiences to date with these patients at the North Carolina Memorial Hospital and to assess the value of the various palliative measures utilized in accomplishing these aims.

Material

This study covers a period of 8 years, from September, 1952, to September, 1960. During this period there have been 1,685 admissions for cancer on the gynecology service, including patients with carcinoma in situ.

Table I reveals that in the past 8 years 638 patients have had a diagnosis of a malignant lesion of the female genitals. Of these, 251 are now dead and 43 are living with either proved or strongly suspected residual cancer. In addition, there were 141 patients with carcinoma in situ for a combined total of 779 patients.

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Indications for palliative procedures

It is imperative that the decision first be made as to whether any treatment instituted will be an attempt at curative or palliative therapy. This requires a thorough knowledge of the pathologic and clinical behavior of the disease process and a sound clinical evaluation of the individual patient. This includes not only the extent of the disease but a number of other factors which must be weighed before a decision can be reached. If and when it has been acknowledged that the malignancy probably is not curable—a decision fraught with pitfalls—it becomes necessary to appraise carefully the symptoms to determine whether some degree of palliation can be achieved. By definition, to palliate means to "ease without curing." The primary consideration in resorting to palliation in the patients reported in this series was a hope that relief of symptoms would be obtained for a reasonable period of time. Prolongation of life, per se, without relief of symptoms, was not an objective of therapy and should be but a secondary consideration. Indeed, prolongation of life, without relief of symptoms, is to be avoided.

Palliation of some form was considered

when the following conditions and symptoms existed: (1) pain, (2) local recurrence, (3) presence of a mass, (4) ureteral obstruction, (5) urinary or bowel fistulas, (6) intestinal obstruction, (7) ascites, (8) hemorrhage, (9) unresectable tumor, (10) bony metastases, and (11) distant metastases.

The criteria suggested by Tod[1] have been followed in the evaluation of the degree of palliation achieved:

Criteria.

No palliation. Either there was complete failure to relieve symptoms or temporary relief was followed by a relatively long period of painful or distressing illness.

Some palliation. There was a period of satisfactory relief of symptoms at least as long as the subsequent painful or distressing illness.

Good palliation. There was a period of complete or almost complete relief of symptoms followed by a terminal illness short in relation to period of relief.

Palliation procedures utilized

Table II summarizes by site the various modalities utilized in this series of patients. It should be mentioned that no method of supervoltage irradiation or perfusion of pelvic neoplasm was administered to any of these patients. Exenteration as a palliative procedure was not performed.

Carcinoma of the vagina and Fallopian tube have not been included because palliative measures have not been indicated in the few patients with these cancers. In addition, palliation in carcinoma of the vulva has been omitted from further discussion because of paucity of patients.

Palliative irradiation. One of the most frequent indications for the use of re-irradiation is the suspicion of recurrence, either by histologic diagnosis or clinical impression. The diagnosis of recurrence by palpation is difficult. This is true particularly in patients with carcinoma of the cervix where one is faced with the problem of trying to differentiate between the changes secondary to irradiation fibrosis, induration secondary to infection, and infiltration due to cancer. While the vast majority of the patients in this series with cervical cancer were treated for obvious palliation, several patients were treated primarily for local recurrence with some hope of cure. For the present they are being considered as patients who qualified for palliation.

Techniques. It is implicit that palliation by radiotherapy should not add a bothersome skin reaction requiring care. The course of treatment should not be protracted since the objective is to produce vigorous, biologic damage to the tumor cells in a short time. In an attempt to do this, published charts of skin tolerance doses have been used with 75 to 85 per cent of this dose delivered in 4 to 8 days with an endeavor made to deliver a tumor dose of 75 per cent of the curative dose, equated on a biologic time/dose relationship. The size and number of the ports used also require consideration. Basically, no attempt to cover all of the tumor-bearing area has been made, but the smallest possible ports or radium needle volume implants to achieve the desired palliation have been used. Oblique and lateral ports are also employed to take advantage of untreated skin areas. No complications have been encountered.

This technique has not been applied to ovarian carcinoma because of the large volume that must be irradiated. In view of the extremely poor results achieved with this technique in ovarian cancer, however, it may be worth while to adopt a more vigorous approach in the future.

When dealing with these discouraging therapeutic situations, one is inclined to agree with Tod[1] that palliation is difficult to obtain and difficult to measure, but its part in cancer therapy is so important that there is need to extend its scope by the improvement of purely palliative techniques.

In Table III the number of patients treated with palliative irradiation is tabulated by the primary sites of the malignancies. If one considers that all patients in this series who are already dead of their disease (251) or are living with recurrence (48) were or are potential candidates for

consideration of palliative irradiation, the incidence of attempted palliation by site and for the entire group of patients with pelvic cancer can be shown (Table III).

Sites.

CERVICAL CANCER. Fifty patients with cervical cancer were considered candidates for palliative irradiation. Table IV shows that the majority of patients with carcinoma of the cervix who are to develop recurrence do so within the first 18 to 24 months following treatment. Seventy per cent of the patients in this series conformed to that pattern, with 49 per cent of the recurrences occurring within 12 months.

Table V tabulates the various indications for palliative irradiation, the number of patients treated for the various indications, and a subjective appraisal of the degree of palliation achieved. Fifty-eight per cent had no palliation, with 20 per cent obtaining fair palliation and 22 per cent good palliation.

Perhaps a more objective approach to

Table I. Pelvic cancer treated at North Carolina Memorial Hospital September, 1952, to September, 1960

	Total seen	*Living without recurrence*	*Dead*	*Living with recurrence*	*Lost to follow-up*
Cervix, invasive	470	246	186	24	14
Endometrium	75	39	20	11	5
Ovary	54	17	29	7	1
Vulva	24	14	9	1	0
Vagina	13	7	5	0	1
Tube	2	0	2	0	0
Total gynecologic malignancies	638	323	251	43	21
Carcinoma in situ of cervix	141	140	1	0	0
Total invasive and pre-invasive malignancies	779	463	252	43	21

Table II. Type of palliative procedures by site

Procedure	*Cervix*	*Ovary*	*Endometrium*	*Vulva*	*Total*	*% of total*
Irradiation	50	20	6	2	78	54
Chemotherapy	1	13	5	0	19	13
Urinary diversion	19	0	0	0	19	13
Fecal diversion	9	3	1	0	13	9
Hypogastric artery ligation	1	0	0	0	1	0.6
Cordotomy	15	0	0	0	15	10
Total	95	36	12	2	145	

Table III. Patients receiving palliative irradiation

	Patients dead or living with recurrence	*Total treated*	*Per cent treated*	*Living*	*Dead*
Cervix	210	50	24	9	41
Endometrium	31	6	19	1	5
Ovary	36	20	56	4	16
Vulva	10	2	20	0	2
Total	287	78	27	14	64

Table IV. Interval between initial treatment and palliative irradiation of cervix

Months after initial therapy	*Patients*	
1-6	8	24/49 = 49%
7-12	16	
13-18	6	34/49 = 70%
19-24	4	
Over 24	15	
Palliative only	1	
Average	17.6 months	
Range	3-224	

Table V. Indications and results of palliative irradiation in cancer of cervix

Indications	*Patients*	*Palliation*		
		None	*Fair*	*Good*
Local recurrence	20	9	5	6
Pain	19	13	2	4
Bony metastasis with pain	4	1	2	1
Mass	6	5	1	0
Distant metastasis	1	1	0	0
Total	50	29	10	11

Table VI. Duration of palliation attained for various indications in cancer of cervix

Months	*Local recurrence*	*Pain*	*Bony metastasis*	*Mass*	*Distant metastasis*	*Total*
No palliation	9	13	1	5	1	29
1-6	3	4	2	0	0	9
7-12	3	1	0	1	0	6
13-18	2	0	0	0	0	2
19-24	1	1	0	0	0	1
Over 24	2	0	1	0	0	3
Total	20	19	4	6	1	50

Table VII. Duration of survival after palliative irradiation in cancer of cervix

Months	*Patients*	
1-6	25	
7-12	13	
13-18	5	43/50 = 86%
19-24	4	
Over 24	3	

	Living	*Dead*	*Total*
Average survival	16	9	10 months
Range	5-38	1-40	1-40 months

the evaluation of degree of palliation is an analysis of duration of relief following therapy. Table VI evaluates the duration of palliation by indication for treatment. As one would expect, reasonable palliation was achieved with the problem of local recurrence. Five of 6 patients with pelvic masses and 1 patient treated because of a pulmonary metastasis obtained no palliation.

Relief of pain is undoubtedly the most important consideration of all indications for palliation. In this series there were 23 patients treated primarily because of pain, including those who had bony metastasis. Fourteen of 23 patients, or 61 per cent, experienced no palliation, and an additional 6 patients experienced relief of pain for a maximum of 6 months. Three patients received good palliation for intervals of 9, 20, and 30 months, respectively. Survival following palliative irradiation is presented in Table VII.

ENDOMETRIAL CANCER. The number of patients with endometrial carcinoma treated with palliative irradiation is small. Table VIII tabulates the three primary indications for therapy and the result achieved. Two of the patients with vault recurrence were treated with radium prosthesis, the remaining 4 with external therapy. Two patients with pain secondary to bony metastasis were considered to have received fair palliation. One patient with vault recurrence is living 6 months following therapy. Five of the 6 patients treated are dead. The average survival was 9 months with a range of 1 to 14 months.

OVARIAN CANCER. Fifty-four patients had ovarian cancer, 36 of whom are dead or living with recurrence. Nineteen of these 36 patients received some form of palliative irradiation. In addition, 1 patient who had a metastasis to the right deltoid muscle and later to the right axillary nodes is included. At the present time, she shows no evidence of recurrence 2 years following radical axillary dissection and postoperative irradiation.

Table IX tabulates the method of therapy, a subjective evaluation of degree of

palliation and the present status of the patients. Seventeen patients received external therapy, 6 of whom had supplemental isotopes or chemotherapy, and 3 patients were treated with radioactive isotopes. Sixteen of the 20 patients, or 80 per cent, were thought to have received no palliation whatever. Three patients were considered to have experienced fair degrees of palliation as judged by relief of pain or frequency of paracenteses for ascites. One patient, described above, is living 18 months following supplementary therapy without evidence of local or distant recurrence. In the 4 patients thought to have received some degree of palliation, the average survival was 14 months, with a range of 7 to 18 months. Sixteen of the 20 patients treated palliatively are dead.

Chemotherapy. There are numerous reports concerning the effectiveness of nitrogen mustard compounds in the palliation of far-advanced malignancy. A number of these deal specifically with ovarian cancer.[2-6] Nitrogen mustard is a cellular poison

Table VIII. Indications and results in palliative irradiation in endometrial cancer*

Indications for treatment	*Patients treated*	*Palliation*			*Living*	*Dead*
		None	*Fair*	*Good*		
Vault recurrence	3	1	1	1	1	2
Bony metastasis	2	0	2	0	0	2
Unresectable carcinoma	1	1	0	0	0	1
Total	6	2	3	1	1	5

*Survival: Average 7 months; range 1-14 months.

Table IX. Types of therapy and results in the palliation in ovarian cancer*

Type palliation	*Patients*	*Palliation*			*Living*	*Dead*
		None	*Fair*	*Good*		
X-ray only	11	9	1†	1	4	7
X-ray and isotope	4	3	1†	0	0	4
X-ray and chemotherapy	2	2	0	0	0	2
Isotope only	3	2	1†	0	0	3
Peritoneum 2						
Pleura 1						
Total	20	16	3*	1	4	16

*Survival—all patients: average 6 months; range 0-18 months; patients in whom palliation was achieved: average 14 months; range 7-18 months.

†Dead.

Table X. Type of cancer treated with chemotherapy

Type of malignancy	*No. of patients treated*	*No. showing improvement*
Adenocarcinoma of uterus	4	1
Adenocarcinoma arising in teratoma of ovary	1	0
Serous cystadenocarcinoma, ovary	2	1
Adenocarcinoma, ovary	4	2
Undifferentiated carcinoma, peritoneal cavity	1	1
Granulosa cell carcinoma, ovary	1	0
Unlisted tumor of ovary	2	0
Mucinous adenocarcinoma, ovary	1	0
Epidermoid carcinoma, cervix	1	0
Pelvic sarcoma, site not stated	1	Unknown
Adenocarcinoma, peritoneal cavity, site unknown	1	Unknown
Total	19	5

and exerts ". . . a specific nucleotoxic action by interfering with chromosomal mechanisms and mitotic division in a manner somewhat analogous to the effects of roentgen rays."[7] Although Spitz was unable to find consistent histologic changes in most of the body tissues, there is almost invariably lymphatic and bone marrow depression following the use of mustards and this feature (i.e., leukopenia and thrombocytopenia) has been used as an index of therapeutic response.[8]

In reviewing the actions of and indications for the use of mustards, Reinhard, Good, and Martin[7] state that among the prerequisites are previous adequate x-ray therapy and skin changes which would preclude further such therapy.

Mustard compounds have been used here in 19 patients with pelvic cancer, of whom 12 had ovarian, 5 uterine, and 1 cervical, and 1 had pelvic malignancy with the primary site unknown. Indications were extended beyond those stated by Reinhard.[7] Several patients had not received x-ray therapy previously but were given cytotoxic drugs immediately after the finding of extensive and unresectable carcinoma. Most patients, however, had received one or more courses of x-ray therapy previously and several had received intraperitoneally a radioactive substance (P^{32} or Au^{198}).

Table XI is a summary of the indications for cytotoxic drugs. Of the 19 patients treated, 7 had recurrent carcinoma after resection of the tumor. Twelve patients were treated because of the finding of unresectable carcinoma at laparotomy. Most of the latter group received irradiation therapy and/or intraperitoneal radioactive material. It is noteworthy that although ascites was present in only 7 patients treated in this group, all 5 of the patients who showed objective clinical improvement were in the group of patients who had ascites. Diminution in the rate of formation of ascites, as determined by a decrease in the number of paracenteses required, or the elimination of their need for several months, was the major beneficial response noted. This appears to be in agreement with most of the larger series of patients reported by various groups.

Table XI. Indications for use of cytotoxic drugs

Unresectable carcinoma	8
Unresectable carcinoma with ascites	4
Recurrent carcinoma with ascites	3
Recurrent carcinoma with distant metastasis	2
Recurrent carcinoma with mass and pelvic or abdominal pain	2
Total	19

Table XII. Cytotoxic drugs used in treating incurable pelvic cancer

Drug used	*Patients treated*	*No. showing objective improvement*
Chlorambucil	3	2
Mechlorethamine and TEM	9	0
thioTEPA	2	1
Cyclophosphamide	4	2*
Tetramin	1	0
Total	19	5

*Two patients were lost to follow-up at the time of this writing.

Table XII shows the drugs used. In reviewing the patients' records, there seems to have been no consistent reason for selecting any particular drug; rather, selection was made at the discretion of the physician in charge. Nitrogen mustard was used in standard doses of 0.4 to 0.6 mg. per kilogram intravenously, but results have been consistently poor. Results with chlorambucil given orally (10 to 30 mg. per day) and triethylenethiophosphoramide (thioTEPA) given in doses as tolerated by the patient appear much better, but in a series this small no definite conclusions can be drawn. Cyclophosphamide (cytoxan) has been used in 4 patients, 40 mg. per kilogram intravenously for 3 days, then 100 to 300 mg. daily as a maintenance dose. A recent report by Coggins and associates[6] indicates that larger doses may be given with benefit without greatly increasing side effects.

All patients have been followed with biweekly leukocyte and platelet counts. Although white counts have been maintained

for weeks at levels between 2,000 and 4,000 c.mm. and platelets have occasionally fallen below 60,000 c.mm., there have been no problems of bleeding or uncontrollable infection. Side effects otherwise have been few and have usually consisted of mild nausea and vomiting. While this has been severe in a few instances, it has been controlled by antiemetics. According to Coggins and co-workers,[6] cyclophosphamide appears to cause less nausea and vomiting and to produce less thrombocytopenia, which was true in this series.

Alopecia has been noted in one patient treated with cyclophosphamide.

Five patients showed objective clinical improvement. One (adenocarcinoma of uterus treated with cyclophosphamide) has required only one paracentesis in 6 months but has since had a course of external pelvic x-ray treatment for a mass imposing on the bladder. A second (serous cystadenocarcinoma treated with chlorambucil) has required no paracentesis since the drug was started 8 months ago but has since required x-ray therapy for a recurrent mass in the pelvis. The third patient (ovarian adenocarcinoma treated with cyclophosphamide) has had no ascites since starting the drug 6 months ago and is living at this writing. A fourth patient is alive with persistent abdominal masses but without having developed ascites (papillary adenocarcinoma, ovary, treated with chlorambucil). She is able to be up and about although unable to carry out routine household chores. The fifth patient (undifferentiated tumor of abdominal cavity treated with thioTEPA) died 7 months after starting the drug but ascites had been well controlled.

Table XIII. Indications for urinary diversion and survival time after diversion

Indication	*No.*	*Survival (months)*	
		Mean	*Range*
Ureteral obstruction	12	2.6	0-9
Fistulas			
Ureterovaginal	1	7	
Vesicovaginal	6	4.3	0.5-11
Total	19	3.4	0-11

Table XIV. Procedures employed for urinary diversion and survival time

Type diversion	*No. done*	*Survival (months)*	
		Mean	*Range*
Ureterosigmoidostomy	5	2.9	0.75-7
Ileal conduit	1	11.0	
Wet colostomy	2	2.2	0.5-4
Pyelostomy	6	1.9	0-3
Cutaneous ureterostomy	5	4.6	2.5-9
Total	19	3.4	0-11

Urinary diversion. A total of 19 procedures for urinary diversion have been done in patients with known incurable pelvic malignancy. All of the patients had a primary diagnosis of cervical cancer. Eighteen were epidermoid carcinomas and 1 was adenocarcinoma. The indications for the various procedures are noted in Table XIII.

The majority of the procedures were performed on patients with obstructive uropathy and uremia secondary to cervical malignancy, and a lesser number were done for fistula formation. That these patients are a highly selected group is obvious inasmuch as ureteral obstruction and uremia accounted for the deaths of most of the 186 patients with cervical cancer who are now dead of the disease. Generally, patients have been selected who were having little or no pain from the malignancy, and whose death from extensive local or metastatic disease did not appear imminent. It is difficult to be enthusiastic about urinary diversion in patients who already are having severe pain from pelvic malignancy, especially when it is apparent that survival time is usually not much increased by the procedure. Whether the procedure is done for fistula formation or obstruction seems to make little difference in this regard. Table XIV shows the various types of urinary diversion procedures that have been utilized. The type of procedure has been selected, of course, on the basis of the specific problem presented by the patient.

In patients who have uremia, especially

those with markedly elevated potassium levels, the simplest possible procedure (i.e., pylostomy) has been selected. In general, consideration should be given to patient comfort and ease of management postoperatively, inasmuch as the possibility of a long survival in this group of patients is virtually nil. Therefore, in spite of the hazard of ascending infection and resulting renal damage, ureterosigmoidostomy has been one of the most commonly utilized procedures in patients whose general condition allows this relatively extensive procedure. All of these patients have died of local or metastatic disease. None was lost because of progressive renal damage due to the procedure. Electrolyte problems, as described in a classic paper by Stamey,[9] have not been encountered in this small group of patients, undoubtedly because of the generally short life span.

The 2 wet colostomies were created in patients having both vesicovaginal and rectovaginal fistulas due to malignancy, and certainly would not be selected as a procedure of choice if any other course seemed feasible.

It is apparent in Table XIV that survival after any of the above procedures has been limited. This is not surprising when one remembers that all of these patients had advanced cervical cancer necessitating the operation. Average survival after diversion has been 3.4 months, and it seems to make little difference which procedure is performed. The authors would prefer, therefore, the least traumatic procedure possible which would leave the patient with a reasonably simple means of urinary disposal. In the future, this probably will consist more frequently of transplantation of one or both ureters into the intact sigmoid colon.

Management of bowel complications

Bowel complications may occur in patients with pelvic malignancy as a result of extension of the disease or secondary to therapy. These complications may be divided generally into three groups: obstruction, fistulas, and irradiation proctitis. It should be noted that, in spite of the large number of bowel complications encountered in this group of patients, relatively few were subjected to surgical intervention.

Although surgical and irradiation complications are mentioned for completeness, the aim is to focus attention on those patients whose complications resulted from spread of the disease.

It will be noted that all patients seen with intestinal obstruction secondary to malignancy were operated upon for relief of obstruction. Most of these operative procedures have consisted of simple sigmoid or transverse colostomy. Only one small bowel obstruction due to malignancy has been encountered. This was relieved by iliocolostomy, bypassing the obstructed area.

Although rectovaginal fistula due to malignancy was a fairly common result of uncontrolled cancer, only 3 patients had operative therapy. Rectovaginal fistula is a late complication of pelvic malignancy. Patients presenting this problem are usually too debilitated from extensive involvement elsewhere for consideration of even simple sigmoid colostomy. For this reason, only 3 of 23 patients have had colostomy performed. Those patients who have survived for a sufficient period of time have learned, with proper training, to manage the colostomies satisfactorily.

Small bowel fistulas present a different and more pressing problem. The liquid, irritating small bowel contents are much more difficult for the patient to control and make the patient most acutely uncomfortable. One may feel obligated, therefore, to offer the patient surgical relief of symptoms by the simplest effective procedure. This may be achieved by bypassing the fistula with implantation of the small bowel into the colon or into the small bowel distal to the fistula.

As in the patients with urinary diversion, survival has been short after bowel operation for residual malignancy. This, of course, would not be surprising in view of the extent of the disease when the complication occurs. In spite of the short survivals, it is

Table XV. Bowel complications and therapy, including survival figures

Complication	*Total*	*No. surgically treated*	*Mean survival after surgical therapy (months)*	*Range survival after surgical therapy (months)*
Intestinal obstruction				
Due to malignancy	9	9	3.5	0.5-12
Due to irradiation	1	1	Living	—
Rectovaginal fistulas				
Due to malignancy	23	3	1.7	0.5-4
Due to irradiation	5	4	All living	—
Postoperative	1	1	0.5	—
Small bowel fistulas				
Due to malignancy	1	1	1	—
Due to irradiation	1	1	10	—
Irradiation proctitis	28	1	Living	—
Total	69	21		

felt that the procedures contributed something in terms of patient comfort and added, in those with intestinal obstruction, a few weeks or months to the patient's life span.

Hemorrhage

The problem of hemorrhage is most often encountered in patients with cervical cancer. No reference to serious hemorrhage from vaginal, vulvar, or endometrial carcinoma has been found in the current literature. Profuse vaginal hemorrhage is a relatively frequent terminal event in cancer of the cervix. The hemorrhage may result either from irradiation necrosis or from friable necrotic tumor. Both present serious problems of management and may prove fatal even in the presence of the most aggressive treatment.

A number of simple procedures has been employed in an attempt to control bleeding and include: (1) suture of bleeding points, (2) electrocoagulation of the cervix, and (3) tight vaginal packing. These methods have been used singularly and in combination.

Hemorrhage which occurs in untreated or incompletely treated malignancy has been controlled best by irradiation either via direct application of radium to the cervix, midline external irradiation, or by vaginal cone therapy. The method selected is dependent upon the pathologic anatomy in each situation. The methods listed above have been used as temporary measures until the irradiation therapy controlled the bleeding.

Bilateral hypogastric artery ligation has been employed with success in one patient. Other workers[10, 11] have reported a high percentage of effective hemostasis by this procedure, which is a relatively simple one technically and may be approached either transperitoneally or extraperitoneally, as described by Daro and associates.[12] The ovarian artery and round ligament should be ligated also in view of the abundant collateral circulation between the ovarian and uterine vessels. This may be a temporary lifesaving procedure in patients with profuse hemorrhage.

Table XVI. Operations performed on the bowel and survival times

Procedure	*No.*	*Survival (months)*	
		Mean	*Range*
Sigmoid colostomy	7	3.2	0.5-12
Transverse colostomy	2	3.0	1-5
Ileocolostomy	2	2.5	1-4
Wet colostomy	2	2.3	0.5-12
Total	13	2.9	0.5-12

Narcotics

In the management of pain all of the usual medications have been employed. It has been a rule to start patients on aspirin and/or phenacetin and to resort to stronger drugs in steplike fashion as the need arose. Codeine has been employed in dosages up to 60 mg. every 3 hours, thence to meperidine or morphine. Chlorpromazine and some of its derivatives are also useful adjuncts in the management of pain. It has been a policy, however, to think of more permanent and effective measures such as cordotomy which in almost every case of uncontrollable pain has been found effective and without serious complication.

Cordotomy

Fifteen patients in this series, all of whom had cervical cancer, were considered candidates for cordotomy. While pain is probably the most common and important symptom of advanced cervical cancer, one finds relatively few articles in the gynecologic literature devoted specifically to the various types of pain which occur in this disease. Before embarking on the subject of indications for, and results of, cordotomy, a portion of this presentation will be devoted to the problem of the types of pain seen in these patients.

Many patients with cervical cancer will have pain at some time during the course of their disease. A careful study of the descriptions of pain experienced by these patients reveals several different types of pain, each with its own pathologic substrata. Relief from some types of pain does not require destruction of some part of the neural mechanism subserving pain because they do not develop into a syndrome of intractable pain. Some kinds are self-limiting and others respond to measures directed at the pathologic lesion causing the discomfort; for example, the removal of a hydronephrotic kidney. There are, however, other types of pain associated with carcinoma of the cervix which clearly point to the need for cordotomy to relief suffering.

Analysis of the pain experienced by the patients in this series with carcinoma of the cervix showed the following types of pain and the implication of each type in so far as the need for cordotomy was concerned. Frequently, two or more types will follow each other and more than one type of pain may be present at the same time. The types of pain are as follows:

1. A common discomfort is the pain associated with irradiation dermatitis. This is self-limiting and usually responds satisfactorily to applications to the painful areas.

2. Involvement of the bladder and rectum cause dysuria, tenesmus, and perineal pain. This type of pain often poses a most difficult problem when cordotomy is under consideration since it may be caused by a reaction to irradiation or by carcinomatous invasion of the bladder and rectum.

3. Thrombosis of the iliac vein or involvement of the pelvic lymphatics by cancer is heralded by rapidly developing generalized edema of the leg. The discomfort accompanying this condition is often mild, even though the edema is refractory to the usual remedies. The presence of iliac thrombosis frequently indicates that the carcinoma has spread to the lymph nodes of the pelvic wall and consequently frequently accompanies involvement of the lumbosacral plexus.

4. Obstruction of the ureter and hydronephrosis is painless in most patients. When not present simultaneously with some other types of pain, it has not been recognized as an indication for cordotomy. The discomfort occasionally caused by ureteral obstruction and hydronephrosis ordinarily responds to the appropriate operative intervention upon the urinary tract.

5. In this series, carcinoma of the cervix rarely metastasized to bone but when it did the spread was to the lumbosacral spine and pubis. The pain was severe and deep in the pelvis, radiating to the back. If pain remains intractable for 2 weeks after a course of radiation to the bony metastasis, cordotomy is required for relief.

6. During the course of its extension, cervical cancer usually invades the lateral walls of the pelvis and ascends along the regional lymphatics to involve the lumbo-

sacral plexus. Often this will produce at least some subjective numbness in the extremity and less frequently weakness and depression of deep tendon reflexes. Frequently, severe and agonizing pain will occur down the leg. At times the pain is in the distribution of the femoral or sciatic nerves, but in many instances it will be an ache deep in the leg as though the pain were in the bone. The type of pain, caused by involvement of the lumbosacral plexus, is a truly intractable pain syndrome and is a clear indication for cordotomy.

Indications for cordotomy. The evaluation and selection of a patient for cordotomy involves many complex factors. A precise statement of the indications, so that they will be of help in making the decision in a particular instance, is difficult. In the appraisal of any patient for whom cordotomy has been requested it must be established first that an intractable pain syndrome exists, and this in itself may be exceedingly difficult. A careful history is necessary to determine which of the various types of pain which this disease can cause is being experienced by the patient. The types of pain for which cordotomy is strongly indicated are those produced by involvement of the lumbosacral plexus, metastasis to bone, and invasion of the bladder and rectum.

The duration and severity of the pain are factors which cannot be disregarded. A cordotomy should not be performed for pain of relatively brief duration, even though it seems likely to be a type which will prove intractable. Yet, when the means are available to give relief, a patient should not be subjected to a prolonged period of agonizing pain with the attending disintegration of personality to determine whether or not it will be self-limiting.

The progression in the use of drugs required to relieve the pain provides some help in selecting the time for cordotomy. As long as salicylates or codeine relieve the pain, cordotomy should not be done, but if other factors are favorable when the step to opiates is made, cordotomy is indicated. Prolonged use of opiates certainly mitigates against a good result but rarely has this been used as an absolute contraindication. Some patients who have been taking these drugs for a relatively long period do not require them after operation.

Expected length of life often is mentioned as an important factor in selecting patients for cordotomy, but actually it is a secondary consideration because of the error in attempting to estimate survival time. Some of the most gratifying results have been achieved in patients who have had relatively short survival time. It is evident that cordotomy is not performed on patients who are in the terminal phase of an illness such as uremia.

Before a cordotomy is performed the patient should understand and be willing to accept the undesirable side effects, such as atonic bladder and occasionally paretic extremities, which sometimes follow the procedure. These should be explained in a manner which will not lead the patient to refuse a procedure which is needed.

A final factor in the decision concerning cordotomy is the patient's general physical condition. While it is not reasonable to expect an ideal surgical risk in a patient who may have been ravaged by neoplastic disease for years, the general condition should be sufficiently good to permit withstanding a major operation. It must be pointed out that the pain should not be allowed to persist beyond the time that the operation can be done safely. Such delay often carries with it the dissolution of personality caused by prolonged suffering and drug dependence.

Procedure selected to relieve the pain of carcinoma of the cervix. Except for the occasional intrathecal injection of absolute alcohol in patients in the terminal stages of disease, the results of which are uneven and will not be reported, anterolateral cordotomy for the relief of intractable pain has been the neurological procedure of choice in this series. No prefrontal lobotomies have been performed. With a single exception, the cordotomy was done in the high thoracic cord. Cordotomy at this level poses no

Table XVII. Analysis of patients having cordotomy and survival time

Patients treated	15
Age range	25-70
Primary site	Cervix, 15
Interval between initial treatment and cordotomy	
Average	25 months
Range	2-63 months
Survival	
Average	5 months
Range	2-11 months
Preoperative palliative x-ray	4 patients
Satisfactory or good palliation	15 patients

Table XVIII. Complications of cordotomy

		Temporary	*Recovery*
Legs			
Paresis, preoperative	4		0
Paresis, postoperative		6	5
Bladder atony		10	3
Paresthesia	2		
Paraparesis, preoperative	1		0

threat of weakness in the arms, can be carried out bilaterally during one operation, and only rarely does the pain of carcinoma of the cervix extend beyond the range of denervation which can be obtained by an adequate section at this cord level. Initially, a few unilateral cordotomies were performed, but in every instance the patient noticed pain on the opposite side soon after operation. This could be anticipated from the behavior of this disease and reoperation was required. Bilateral sections are performed routinely now.

Results of cordotomy. Cordotomy has been performed in 15 patients with intractable pain caused by carcinoma of the cervix.

Of the types of pain discussed above, 14 patients had involvement of the lumbosacral plexus, 4 had involvement of the bladder and rectum, 2 had thrombosis of the iliac vein, and 1 had osseous metastasis. Ten patients had only one type of pain and 5 had two types. Only 1 patient had no involvement of the lumbosacral plexus. She suffered from invasion of the bladder and rectum.

All 15 patients gained complete relief from the pain for which the cordotomy was performed. One patient, following cordotomy, developed chest pain before death from pleural metastases which were outside the level of the cordotomy. Most of the patients required no opiates. In a few patients, however, there was ill-advised return to these drugs, apparently because of a general feeling of lack of well-being rather than any specific type of pain.

In 10 patients the level to pinprick remained high and in 4 it dropped lower than desirable, but in none did pain return.

Complications. The incidence of some paresis of the legs in patients with previously normal power was high. It occurred in 6 patients, of whom 5 completely recovered. Four patients had moderate paresis in one or both legs before operation and this weakness seeemed to be increased by cordotomy. None of these recovered. One patient had a severe paraparesis before and after operation.

Following operation the urinary bladder was atonic in 10 patients. Only 3 recovered sufficient function to permit removal of the indwelling catheter. Three patients had bladder atony before operation and 1 had an ileal conduit. The incidence before operation of some degree of involvement of the neural mechanism of the bladder may be greater than indicated here and may account for the poor rate of recovery of bladder function.

Two patients had paresthesia below the level of the cordotomy, but this was not troublesome and was regarded as preferable to the pain.

Summary

1. A series of 638 patients with invasive gynecologic cancer, seen during an 8 year period, has been reviewed and emphasis directed toward the problem of palliation in these patients.

2. The indications for palliation in this series have been presented along with the various palliative measures utilized and the results obtained by each.

Conclusions

1. Since the majority of patients with pelvic cancer are not cured, it behooves the physician to devote significant effort to perfecting better methods of palliation until more effective tools of achieving higher rates of cure are developed.

2. The decision as to whether or not palliation is indicated may be tempered by the experience and philosophy of the individual physician. Any form of palliation should be directed toward relief of symptoms rather than toward prolongation of life, which, without relief of symptoms, is to be avoided.

3. Palliation which carries with it a significant risk of major complications or death in a given patient is to be avoided.

4. Palliative procedures in the therapy of pelvic cancer, in general, do not achieve their objective in most patients; many patients must be treated to bring about palliation in a few. This is justifiable only if the methods of palliation are not attended by a high incidence of complication in those patients who do not respond to the treatment.

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Discussion

Dr. C. Paul Hodgkinson, Detroit, Michigan. From the challenge of the first sentence that the majority of women with pelvic malignancy are not curable to the candid admission in the last statement that most palliative measures fail, this paper is a frank and honest appraisal of the results obtained with various palliative measures used in advanced malignancy of the pelvis.

To most the task of affording symptomatic relief for physical conditions which cannot be improved is taxing and unrewarding. Anything done is a compromise. Sometimes one's conscience finds difficulty in differentiating between palliation of the symptoms and prolongation of the agony of progressive malignancy. Too frequently additional treatment represents procrastination, not palliation.

We have used direct arterial perfusion with aminopterin for recurrent pelvic malignancy. The procedure required laparotomy to place fine plastic catheters in the internal hypogastric or the superior hemorrhoidal arteries. Aminopterin, 50 mg. in 1,000 c.c. normal saline containing 50 mg. heparin, was administered over 24 hour periods by metered pumping. The procedure was continued until the peripheral blood and bone marrow showed evidence of dangerous depression. In one patient the procedure was maintained for 21 days. Two patients with recurrent carcinoma of the cervix and one with recurrent carcinoma of the rectum were treated. All had compound rectovesicovaginal fistula and transverse colostomies, and one had an ileal conduit for diversion of urine. All patients claimed to have received some subjective relief from pain. In one patient with carcinoma of the rectum the duration of the relief lasted only 2 weeks. One patient with carcinoma of the cervix has died. The other patient with recurrent carcinoma of the cervix after being subjected to radical hysterectomy, radium, and external irradiation 8 years previously showed both subjective and objective evidence of improvement. A narcotic addict when first observed, she has lived in apparent comfort without resort-

ing to narcotics after receiving 610 mg. aminopterin by direct perfusion into the superior hemorrhoidal artery over a 12 day period in February, 1960. She gained from 114 to 158 pounds in 1 year. Although the pelvis contains considerable malignancy, there has been no apparent extension.

I can readily agree that urinary diversion by wet colostomy is not satisfactory palliative therapy, and its use should be avoided. For this reason I have not employed uterosigmoidostomy for urinary diversion because too frequently the rectum becomes involved subsequently in fistula formation. In my experience, urinary diversion by ileal conduit was handled more easily by the patient, and it was associated with fewer complications.

When diversion of feces is necessary, high transverse colostomy has been the preferred method. If the objective of colostomy was to eliminate continued contamination of rectal fistula, it was found important to separate the ends of the colostomy loops for a distance of at least 20 centimeters. Juxtaposed bowel loops, or a partially cut-through bowel, offered no relief because the distal loop readily aspirated the fecal contents from the surface of the abdomen.

The stand the authors took on cordotomy was commendable. Their emphasis placed upon the necessity of differentiating visceral from somatic pain was practical and important. They pointed up the shortcomings of protracted morphine administration by stating that they were in favor of cordotomy for permanent relief. With that statement few will disagree. The cravings of iatrogenic narcotic addiction superimposed upon incurable pelvic malignancy is a double state of misery. J. P. Pratt insisted many years ago that the physiologic state most appreciated by the patient hopelessly afflicted was that of sleep. Long-acting barbiturates administered in sufficient amounts to induce a state of arousable somnolence is far better therapy than narcosis from morphine, which is increasingly difficult to maintain because of rapidly acquired tolerance. Patients, in the despair of their final days, prefer tranquil sleep to the insatiable cravings of narcotic addiction.

Dr. Frank R. Smith, New York, New York. The management of a patient who is a candidate for palliative treatment consists first in a re-evaluation of what has been done by the group who considered her incurable or, better yet, evaluation by a new group of doctors who may reverse the original opinions.

After re-evaluation the management should consist of reoperating more radically if the first operation was incomplete. Eighty per cent of patients with carcinoma of the ovary presenting themselves at Memorial Hospital had had either an incomplete operation or a simple exploratory celiotomy with biopsy. Radical operation for previously untreated, neglected patients, have a 5 year salvage of 10 per cent by exenteration at Memorial Hospital, New York.

Recent irradiation should be completed if previous irradition has been inadequate. Irradiation for untreated radiosensitive tumors, such as dysgerminoma, psammoma, and adenoacanthoma, may give striking results. Re-irradiation for residual or recurrent carcinoma after primary adequate irradiation is most disappointing and of little or no value.

Various palliative procedures must come under consideration for special symptoms. These may be one of the following:

1. Surgical relief of obstruction by short circuit anastomosis, cecostomy, or colostomy.
2. Cautery or surgical removal of fungating lesions.
3. Irradiation with radioactive isotopes for reduction of ascites or pleural affusion.
4. Chemotherapy with various compounds, such as thioTEPA, etc. (There are more than 100,000 formulas in the National Registry that have been tested. No patient has been cured by them.)
5. Perfusion which may be symptomatically impressive. No authenticated cure has been reported.
6. Cordotomy for pain. This should be performed only if it is estimated that the patient has 3 months or less to live. Subthecal alcohol injections are simpler to perform and somewhat less effective, but may be repeated.
7. Various analgesic drugs and tranquilizers. Hypnosis is not a remedy for pain but may help morale. Opiates should be used as a last resort but not longer than for 1 to 3 months of terminal care.

We should be sure that the therapy selected is doing something *for* the patient and not just *to* her.

Dr. Joseph W. Baggett, Fayetteville, North Carolina. My experience on this subject is strikingly different from the author's and the two

previous discussants'. I have practiced in a town of around 50,000 population in North Carolina with two small community hospitals—the total bed capacity of around 300. I am one of 4 gynecologists and we have 8 general surgeons, so my experience is limited and also the problems are not as many.

In a review of my cases over a 9 year period, 1951 to 1960, of pelvic cancer, I found a total of 73 cases. They were classifiable as follows: squamous cell carcinoma of the cervix, 57; adenocarcinoma of the fundus of the uterus, 8; ovarian malignancies, 3; carcinoma of the vulva, 2; carcinoma of the rectum and sigmoid with gynecological aspects, 2; sarcoma of the uterus, 1.

Of the 57 cases of squamous cell carcinoma of the cervix, 17 fell into the group of squamous cell carcinoma in situ. Of the 40 remaining cases, 14 were treated by Wertheim radical abdominal hysterectomy with pelvic lymph gland dissection; 26 were treated by radium and x-ray therapy of the accepted standards in conjunction with radiologists. Nine deaths have occurred in this group of 40. Palliative therapy was attempted in all 9 cases. Recurrent growths occurred in 7 of the 9 patients and a second course of radiation was resorted to. No apparent clinical improvement was noted in any of these patients, but we did have rather extensive complications arising from these attempts at palliation.

Four of these patients had severe vaginal hemorrhages, two being fatal. Two patients developed vesicovaginal fistulas and one patient had intestinal obstruction. The vaginal hemorrhage in 2 patients was controlled by packing, but death followed within a month or 6 weeks of urinary obstruction. One patient developed an intestinal obstruction which was relieved by transverse loop colostomy and she survived 3 months, relatively free of symptoms, to die of uremia.

Of these 9 patients with squamous cell carcinoma of the cervix, equally divided into Clinical Stages II, III, and IV, the causes of death were as follows: 5 of uremia due to extension of the growth in the pelvis, 2 of fatal vaginal hemorrhage, 1 of a massive gastrointestinal hemorrhage, and 1 of a pulmonary hemorrhage due to metastatic lesion in the right lung.

Two deaths have occurred in the patients with ovarian cancer, each complicated by intestinal obstruction and ascites. The average survival of these patients was less than 18 months. Each died in less than 4 months after colostomy was done to relieve intestinal obstruction.

One death occurred in a patient with carcinoma of the rectum which extended into the vagina. She had a posterior resection including the uterus, vagina, rectum, and a transverse colostomy. This was done as a palliative procedure and I feel we obtained good results. She survived 9 months relatively free of the disease and died in liver failure.

One death due to adenocarcinoma of the fundus of the uterus occurred in the 8 cases of this disease. This patient died within 2 weeks of the onset of symptoms and after being under observation only 3 days. She died of a metastatic lesion to the brain before therapy was instigated or diagnosis made.

The one patient with sarcoma of the uterus survived only a total of 10 months. She died of intestinal obstruction with generalized carcinomatosis. No palliative therapy was recommended.

There was no attempt in the patients with squamous cell carcinoma to relieve the urinary obstruction. It was the clinical impression that these patients had extensive disease involving the whole pelvis and were in a terminal phase. The average rate of survival of these patients was from 1 to 3 months after the recurrent growth was noted.

In reviewing these patients in my group and also in reviewing the statistics of Dr. Palumbo's paper, one cannot help but be impressed with the futility of treatment. Most of my patients lived less than 18 months from initial diagnosis and instigation of accepted therapy for their disease. In my group, attempts at palliative therapy, chiefly by radiation, appeared to have no influence on the course of the disease and only created other complicating factors to treat—such as vaginal hemorrhage, fistulas, and intestinal obstruction. Colostomy was resorted to in the cases of intestinal obstruction and was effective in relieving the patient's obstruction but contributed very little to the survival of the patient.

One must consider that the "host resistance" to the disease will be the determining factor. We should make a greater effort to evaluate the effectiveness of radiation during the primary course of therapy and pick out the cases that are resistant to radiation and offer these patients the alternative of radical operation.

Dr. Waverly R. Payne, Newport News, Virginia. Many years ago, Dr. Jean Paul Pratt presented a paper at a meeting of the Southern Medical Association in New Orleans, emphasiz-

ing the importance of dehydration in the management of terminal cancer. He stated that if fluids were not forced or were even restricted the patient would require much less narcotic medication. Since that time, approximately 25 years ago, I have followed his suggestions implicitly and am more and more convinced of the value of that course of treatment.

I usually discuss my plans with the patient's family explaining to them the inadvisability of intravenous fluids, forced feedings, etc., and I find that as a rule they are most cooperative. As an example, I might cite a patient with terminal carcinoma of the uterus who had been getting ¼ grain morphine every 3 or 4 hours day and night and also large amounts of intravenous fluids. She was definitely addicted to morphine. After discussing the matter with the family, advising them to keep as quiet as possible while visiting the patient, I reduced the fluids to as small an amount as possible. I was myself amazed that the medication for this patient was finally reduced to 1 mg. of racemorphan every 12 hours and yet she was kept perfectly comfortable.

DR. PALUMBO (Closing). Exenterations have not been done for palliation. Those which have been performed with reasonable hope of cure have not been included in this series. I could not agree more with what Dr. Payne has said. I believe I am not misquoting when I say that even the Roman Catholic church recognizes that prolongation of life, per se, is not mandatory.

The validity of Sampson's theory of endometriosis

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IN FEBRUARY, 1958, the preliminary report of experimentally produced endometriosis in the human was given by this author of the work done with Edwards.[1] Since that time the work has continued with further success. A brief review of the thoughts and theories of the histogenesis of endometriosis will be given. Also a brief review of this experiment concerning the problems in its development and technique will be given.

There have been three credible theories of the histogenesis of endometriosis. The most widely accepted theory has been that of Sampson,[2] describing the transtubal regurgitation and implantation of desquamated endometrium. Nearly equally as widely accepted has been that of celomic metaplasia. Third, there is that sound belief that endometriosis may be started by the "benign metastasis" via lymphatics and the blood stream of desquamated endometrial fragments.[3]

Accurate gross pathologic descriptions indicated that endometriosis, although not recognized as an entity, dates back to 1859.[4] Russell[15] in 1899, having found endometrial glands in the ovary, suggested a theory of growth from cell rests of the Müllerian duct. Sampson in 1921 gave, to that date, the most comprehensive description of the condition, coined the word "endometriosis," and speculated about its origin. Review of his interesting paper shows that he really had three thoughts at the time. He suggested that the spread of endometriosis in the pelvis was likely to be due to the rupture of endometrial cysts of the ovary, or of other sites of implantation, with dissemination of viable particles to new sites. Also he strongly entertained the idea that celomic metaplasia, as had been suggested in 1909 by Iwanoff and Meyer,[6] was a plausible explanation. But most important, he suspected the possibility that fragments of the menstruating endometrium, regurgitated from the fimbriated end of the tube in a retrograde manner, could implant within the pelvis and give rise to endometriosis. The latter thought, though logical, hinged on the fact whether the shed endometrium was viable and could grow at an implantation site. In the following 20 years there was more evidence set forth to support his theory but no proof of the viability had been made. The theory of celomic metaplasia championed by Novak[7] gained in popularity and acceptance because this could explain the development of endometriosis at sites where direct implantation could not occur, such as the umbilicus, inguinal lymph nodes, etc.

In 1940, in the twentieth anniversary edition of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, Sampson[8] wrote his paper on the "Development of the Implantation Theory for the Origin of Peritoneal Endometriosis." His theory had been challenged and it was then that he eloquently stated, "If

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bits of Müllerian mucosa carried by the menstrual blood escaping into the peritoneal cavity are always dead, the implantation theory, as presented by me, also is dead and should be buried and forgotten. If some of these bits are even occasionally alive, the implantation theory also is alive." Thus, the fundamental weakness or missing link in the theory of Sampson admittedly was the inability to demonstrate that menstrually shed fragments are viable.

Tissue cultures by Cron and Gey[9] in 1927 were suggestive that there was viability, and this was more conclusively proved in 1953 by Keettel and Stein,[10] who successfully grew, in vitro, both stromal and epithelial elements of human endometrium for a short period of time.

TeLinde and Scott[11] in 1950, reported their experiment on the Rhesus monkey in which the menstrual flow was shunted into the abdominal cavity or abdominal wall. Endometriosis developed in several animals. These experiments were all indicative that shed endometrium might be viable, but the problem still remained as to whether the cells in the human could transplant to another site, flourish, and cause endometriosis in the host.

Material

In 1949, it became apparent to this investigator that it might be possible to prove Sampson's theory or to cast even more doubt on its credibility by an extensive experiment in humans in an attempt to create endometriosis. If it were possible to develop a harmless technique of collection of the menstrual material and then to implant this material at a site for observation, it might be possible to establish an endometrioma. Admittedly, the approach was at first negativistic. After several trials with comparatively complicated collecting devices, the one finally chosen was the simplest and most satisfactory. Then studies were made bacteriologically and cytologically of the shed material that was collected with this apparatus and technique. Cultures made of the material were negative in both aerobic and anaerobic environment for pathogenic and nonpathogenic organisms that might have been present in the patient or as contaminants. Brief thought was given to the possibility of menstrual toxin, but this was dismissed. Cytologic studies were made of the sediment and supernatant portions of the centrifuged specimen by both wet smear and Papanicolaou techniques. Fragments of tissue, apparently viable, were found in the sediment.

The cases for the experiment were selected from women, both white and Negro, of the charity service of the Grady Memorial Hospital of Atlanta. All of the patients selected were to have been scheduled for laparotomy at a subsequent date for an apparently benign condition, such as myomas of the uterus. It was determined that the operation could be safely postponed for the given length of time necessary for the growth of the shed endometrial fragments. No patients were chosen who had any suspicious menstrual irregularities or evidence of active pelvic inflammatory disease.

Of the great volume of patients screened through the several years of the experiment, 85 were found who seemed to qualify. Of this number, about half either failed to cooperate or refused to participate. Thirty-two cooperated and were admitted for study. Of this final group, 15 have been studied while the remaining 17 were found to be unsatisfactory because of scanty flow, failure of the collecting device, or an obvious break in aseptic technique. The attrition of the cases to be studied was at times discouraging.

Criteria

The criteria to be satisfied, as given in the preliminary report,[1] are very important and are herein repeated: (1) the experiment had to be harmless to the patient; (2) the endometrial fragments were to be "shed"; (3) the endometrial cavity could not be invaded for collection of the specimen; (4) the specimen had to be collected by natural flow by gravity and without trauma; (5) the site of implantation had to be extracelomic, extragenital, and at a site where no other operation had been performed; (6) the site of

Table I

Patient and hospital No.	*Age*	*Race*	*Days elapsed after implantation*	*Incidental findings*	*Results*
1. E. E. G. (200964)	37	Negro	110	Myomas of the uterus	Nodule of scarring and gland ascini developed at site of implantation. The epithelium was cuboidal and the stroma questionable
2. Q. D. (383598)	34	Negro	117	Myomas of the uterus	Negative
3. W. K. (380538)	40	Negro	—	Myomas of the uterus	Unsatisfactory—local cellulitis at site of implantation
4. A. H. (248301)	38	Negro	179	Myomas of the uterus	Negative
5. N. S. (176154)	38	Negro	150	Myomas of the uterus	Negative
6. M. H. (373760)	40	Negro	183	Myomas of the uterus	Nodule of scarring with foreign body reaction at site of implantation
7. M. T. (A254000)	25	White	175	Myomas of the uterus	Endometriosis developed at site of implantation
8. C. C. (249507)	32	Negro	195	Myomas of the uterus	Negative
9. J. W. (C10991)	34	Negro	99	Myomas of the uterus	Lymphocytic aggregate with small amounts of hemosiderin deposition
10. L. S. (C30507)	32	Negro	126	Myomas of the uterus	Negative
11. G. V. (C37161)	33	Negro	107	Myomas of the uterus	Fibroareolar tissue extravasated blood
12. D. M. (S602543)	37	Negro	91	Myomas of the uterus	Endometriosis developed at site of implantation
13. E. W. (C86983)	36	Negro	94	Myomas of the uterus	Negative
14. F. G. (C65718)	36	Negro	119	Myomas of the uterus	Fibroareolar tissue with hemosiderin laden macrophages
15. M. F. (C31458)	38	Negro	122	Myomas of the uterus	Negative

implantation had to be apart from the expected drainage routes of the pelvic lymphatics; (7) the period for growth had to be 90 days or more; (8) microscopic evidence of both glandular and stromal elements had to be demonstrable.

Method and procedure

The technique of the collection and injection of the specimen has remained unchanged from the preliminary report.[1] Thus, it will not be repeated at present. No further complications have been encountered.

Results

Fifteen cases have been studied by injection and laparotomy (Table I). Case 3 was unsatisfactory for study. Cases 7 and 12 showed gross and microscopic evidence of endometriosis at the sites of implantation. In

Fig. 1. Low-power photomicrograph of endometrioma.

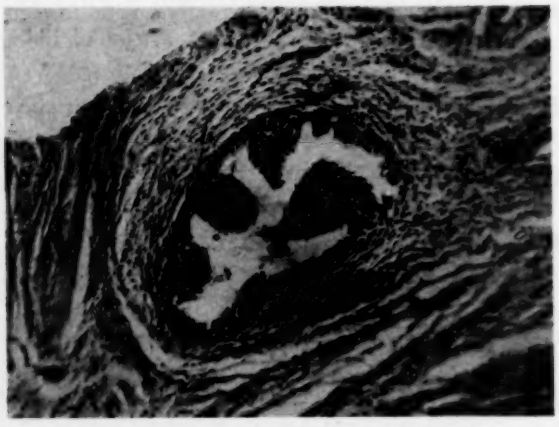

Fig. 2. High-power photomicrograph showing typical gland epithelium, stroma, and dense scarring of endometriosis.

4 other cases, local tissue study showed some reaction of interest. Although none of these latter 4 cases conclusively satisfied the criteria for the microscopic diagnosis of endometriosis, there could be noted evidence of scarring, hemosiderin-laden macrophages, and an occasional small gland ascinus with an atypical epithelium. It is thought that these could be evidence, certainly not as conclusive as in the Cases 7 and 12, of endometriosis. It is recognized also that this could be tissue reaction to the material injected.

One would wonder why every case would not be positive for growth of the endometriosis. It could be for one or many reasons:

1. Simple failure of the endometrium to shed viable cells during the period of collection.

2. Local tissue reaction at site of the implantation where phagocytosis could destroy the viable cells. This reaction may vary in individuals.

3. An unknown factor of host acceptance or rejection of transplanted endometrial tissue. Speculation on this might suggest why a certain type individual or even race is more prone to have endometriosis develop, while others might never develop the condition.

Case reports

Case 7. M. T., was a white, married nulligravida, aged 25 years. Her chief complaint was pelvic discomfort due to a large uterine myoma (16 cm.). Implantation was done on March 1, 1957, and excision performed Aug. 22, 1957, or 175 days after implantation.[1]

Case 12. D. M. was a 37-year-old Negro woman whose chief complaint was pelvic discomfort due to myomatous uterus. Implantation was done on Jan. 11, 1960, and excision was performed on April 11, 1960, or 91 days after implantation. The specimen showed gross evidence of small brownish areas in the scar tissue. It may be seen microscopically that both epithelial and stromal elements were present and encased in rather dense scar tissue (Figs. 1 and 2).

Summary and conclusions

An experiment has been successfully carried out in which endometriosis was created at a site of implantation. This was done with use of shed endometrium of the human which was implanted within the host at a site selected where gross and microscopic observation could be subsequently made. Thus, in at least 2 cases, endometriosis was grown in vivo in the human, proving that the fragments of shed endometrium are viable. The keystone of Sampson's theory of the histogenesis of endometriosis as applied to the human has been established.

This experiment is submitted as evidence that Sampson's theory is valid—that shed endometrium may be implanted within the host to cause endometriosis.

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Discussion

Dr. Louis M. Hellman, New York, New York. In doing tuboplastic operations one of the standard techniques to discover the site of blockage has been to inject methylene blue into the uterine cavity under pressure. There is evidence that this methylene blue sometimes passes through the uterine vein and is also picked up in the lymphatics and can be seen as far lateral as the pelvic wall. This seems to me to indicate that the blood-borne or the lymphatic theories of endometriosis can still stand intact.

There is one aspect of Dr. Ridley's experiment on which I would like to speak. This concerns the moral implication of human experimentation. In bygone days this subject was not considered very seriously. The moral aspect was left entirely to the judgment of the individual physician. However, in recent years in this country we have had committees both of hospitals and of the Federal government to examine experiments. As far as the Federal government goes, a great deal of experimentation in medicine has been supported by funds from the National Institutes of Health. As a result, the question of human experimentation has been examined and re-examined by the committees making the grant awards. A few years ago an editorial in *Science* appeared on this very question.

Experiments involving humans may be divided into two large groups. One is where the experiment can possibly do a particular human or group of humans a great deal of good. It is not about the problem of this group that I wish to speak, for the moral judgment issue here is quite different. In the other group the experiment is designed to advance human knowledge, but may possibly not do the individual on whom the experiment is being performed any immediate good. I believe that this latter type of experiment is important but I also believe that such experiments should be very carefully considered and planned. At the present time it is impossible to give grants for experimentation on pregnant women when radioisotopes are used. Also many other areas of human experimentation are disappearing because of the fear of legal suit. I believe that this is important to all of us for, if this vital avenue of research becomes completely closed, medical advances may be greatly slowed.

The reason I am talking about this is that I think that Dr. Ridley's criteria for his experiment indicate so well the conditions that one must consider in order to carry on any type of human experimentation. In the first place, he not only had the permission of the patients but they were coinvestigators in his experiments and knew exactly what was going on. In the second place, within reason his experiments were not harmful to the patient. Third, Dr. Ridley so designed his experiments that not many were necessary to prove the point. I think that this latter is all-important; namely, that if one is to do human experimentation it should have a precursor animal experimentation where the questions to be asked are clearly defined. Then one or two human experiments may yield the final and definitive answer to the question. This has apparently been the course followed in the investigation of the source of endometriosis. Furthermore, in spite of the animal experimentation of Scott, no amount of such investigation could have given us the answer as far as the human being is concerned.

Dr. Robert B. Greenblatt, Augusta, Georgia. Dr. Ridley has proved to us that shed endometrium is viable and that it can take root

and grow when transplanted as it did in the one white and one Negro patient.

What is difficult to understand is why the endometrium failed to implant itself in the other 14 Negro women. It is unfortunate there were not more white patients in the series to confirm a concept of racial immunity.

Does our national culture have anything to do with the high incidence of endometriosis in our white population and its very low occurrence in the Negro race? That race is not the main factor is apparent from the fact that endometriosis is found, it is said, with far less frequency among the Scandinavians, the French, and the Germans. Could one postulate that in the United States our middle class morality allows sexual experimentation to go so far and no further, so that pelvic congestion plays a role predisposing to the development of endometriosis?

DR. W. VERNON SKILES, Atlanta, Georgia. This study is a continuation by the author of his previous work. The first study contained 8 cases—in one of which endometriosis developed. It is quite interesting that the ratio of successful implantation is the same in both groups. Hypothesizing such a factor of host acceptance or resistance of the transplant certainly calls for the author to pursue his investigation further.

The critical criteria set forth in this experiment have been met and are the crux of the argument which makes the experiment valid. Sampson's theory is now a fact because "shed" endometrial tissue does live, at least some of the time. Yet, no one theory of the histogenesis of endometriosis seems applicable to all cases.

DR. RIDLEY (Closing). We would like to carry out further investigations in younger individuals. However, our available clinical material at the Grady Memorial Hospital was predominantly in the age group of the fourth decade. The presenting complaints were usually those of the uterine myomas, and the majority of the patients were Negro. We had wished to get equal numbers of patients from the white and Negro races, but this proved to be impossible.

I am glad that Dr. Hellman has emphasized the importance of great care and circumspection in any human experiment. All dangers must be eliminated. Actually, the first 3 years of the experiment, from 1950 to 1953, were taken up with perfecting a safe and dependable technique and apparatus for collecting and implanting the specimen.

Lymphocele following lymphadenectomy

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WE DERIVE our interest in the lymphocele largely from the possibility that it may be a new lesion. The novelty of the lymphocele is uncertain because it may have existed in the past without being recognized. Because lymphocele has appeared only recently in the literature and the number of cases reported is small, there are still many unanswered questions concerning its frequency, pathogenesis, diagnosis, symptoms, and treatment and the disability it can cause.

Both "lymphocele" and "lymphocyst" have been applied to the mass we are describing, although neither name is etymologically ideal.

Lymphocele was first described in the American literature in 1958. Gray and associates[1] described the lymphocyst they found in 9 of 55 pelvic lymphadenectomy patients who had been previously treated by radium and external radiotherapy for carcinoma of the cervix.

There is only one other report on lymphoceles in the American literature. Rutledge and associates[2] reported lymphocyst developing in 68 of 281 patients following pelvic lymphadenectomy—an incidence of 24 per cent.

It is puzzling why lymphocele has not been mentioned earlier since the lymphadenectomy operation has been done for many years. There are two possible explanations for this. One is that the lymphocele may have been present but not recognized. The other is that in recent years the lymphadenectomy has become a more extensive operation and that this may predispose to lymphocele formation.

The incidence of the reported cases of lymphocele varies widely (Table I). Kimbrough[3] reported only one lymphocele when 87 women with Stage I, II, and III carcinoma of the cervix were treated with primary retroperitoneal node dissection followed by complete irradiation. Claiborne and coworkers[4] reported no lymphoceles in 62 cases of retroperitoneal node dissection for carcinoma of the cervix.

Lock and co-authors,[5] in a group of 22 patients with Stage I carcinoma of the cervix treated by radical hysterectomy and lymphadenectomy, noted transient small lymphoceles in only 2 patients.

Mori[6] reported a lymphocele frequency of 49 per cent.

The lymphadenectomy operation

We wish to describe 12 patients who had lymphoceles in our experience with 95 pelvic lymphadenectomies at the University of Miami–Jackson Memorial Hospital. These operations were performed between July, 1956, and the end of 1960.

We can divide our 95 patients into two groups, each with a considerable difference in frequency of lymphocele formation.

The first group of 54 patients (Series A) were those who had a transperitoneal lymphadenectomy followed by intracavitary

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Table I. Incidence of lymphoceles following lymphadenectomy

Author	*Incidence (%)*
Claiborne, Thornton, and Wilson	0
Kimbrough	1
Lock, Greiss, and Blake	5
Ferguson and Maclure (Series A, 19%) (Series B, 5%)	13
Gray, Plentl, and Taylor	16
Rutledge, Dodd, and Kasilag	24
Mori	49

radiotherapy, usually started under the same anesthetic. These were patients with clinical Stage I or II carcinoma of the cervix who underwent the lymphadenectomy as an adjunct to the radiotherapy. Ten (19 per cent) of these 54 patients developed lymphoceles. The evaluation of lymphadenectomy as a supplement to radiotherapy in these cases will have to be postponed until more time has passed. Then it will be necessary to match the seriousness of the lymphocele and other complications with the improvement, if any, in prognosis for the carcinoma added by the lymphadenectomy. Forty-eight of the 54 patients are alive and presumably free of disease at this time.

The second group of 41 lymphadenectomy patients (Series B) were a miscellaneous group in which each patient had a lymphadenectomy plus some other operation, such as a radical hysterectomy, a simple hysterectomy, or a radical vulvectomy. Two (5 per cent) of these 41 patients had lymphoceles. Series B included patients who had an extraperitoneal lymphadenectomy as well as those who had a transperitoneal lymphadenectomy. The technique of the lymphadenectomy was essentially the same in all of the Series B patients.

The patients with lymphadenectomies are divided into these two groups because the incidence of lymphocele was much greater in the Series A group of patients who had the transperitoneal lymphadenectomy and intracavitary radiotherapy (Table I). The feature of the Series A cases which distinguished them more than anything else was the meticulousness of the lymphadenectomy. With the lymphadenectomy the major operative procedure, there was time and the inclination to do a much more thorough dissection than in the Series B miscellaneous group. We do not wish to imply that the Series B lymphadenectomies were hasty or incomplete operations.

The dissection in all 95 cases extended from the bifurcation of the aorta or a point 1 or 2 cm. above it to the point where the external iliac vessels disappeared into the lower extremity. No effort was made to ligate the tissue at the lower end of the dissection, a maneuver that might have prevented some lymphoceles. All possible lymphatic and areolar tissues were excised from the dissected areas and vessels, including the common iliac arteries and veins, external iliac vessels, the hypogastric artery, and the uterine artery, to the point where it disappeared over the ureter. The obturator fossa was thoroughly emptied and the presacral area was investigated for the presence of lymph nodes.

Description of the lymphoceles

Once we became familiar with the characteristic feel of a lymphocele on bimanual examination, the diagnosis was not difficult and the lymphocele could be distinguished from the nonfluctuant induration in the iliac fossa and broad ligament found after lymphadenectomy. A slight prominence of the abdominal wall above and parallel to the inguinal ligament was usually seen and palpated. If there was any tenderness in this mass generally it was mild. The upper limit of the mass most often has been inferior to the anterior superior spine of the ilium, but some of the larger masses have extended higher. On bimanual examination it was clearly recognized that the mass contained a fluid. A few of the lymphoceles have descended low enough in the pelvis to cause a bulging of the lateral vaginal wall that could be felt by manual vaginal examination and seen during speculum examination. This extension into the paravaginal space on two

occasions has permitted aspiration of the lymphocele contents through the vaginal wall.

With lymphoceles we always found there was great edema of all of the tissues surrounding this collection of fluid, giving the false impression that the mass was much larger than it actually was. The most evident edema was in the muscles of the abdominal wall overlying the lymphocele. Frequently when pressure was exerted on these muscles, as in clamping or retraction of tissues during surgical drainage of the lymphocele, edema fluid exuded from the muscles.

Two puzzling cases of incorrect diagnosis of lymphocele were encountered. In one patient a thorough exploration was done 3 weeks after lymphadenectomy because of a mass that was typical of a lymphocele. Instead of a lymphocele we found the usual soft tissue edema associated with lymphoceles. The mass disappeared rapidly after exploration. The second patient was well for 6 months after lymphadenectomy until she suddenly became febrile and had an abdominal mass similar in size and location to a lymphocele except that it appeared to be an abscess. The mass was explored as if it were a lymphocele. We found the same edema of the tissue as we note about the lymphocele. Instead of a lymphocele, a 2 ml. pocket of pus was found anterior to the external iliac vessels. The region was drained and recovery was prompt.

The estimated volume of the lymphocele fluid varied considerably. At least 2 were so small that drainage was considered unnecessary. The average amount of measured fluid found in the lymphocele was 300 ml. One patient had 700 ml. removed by vaginal needle aspiration, and 4 days later 500 ml. was removed by abdominal extraperitoneal drainage; some of this probably was reaccumulated fluid.

There has been considerable difference in the size and extent of the lymphocele. Invariably a portion of the cavity was located anterior to the external iliac vessels. The smaller lymphoceles lay exclusively in this position between the external iliac vessels and the abdominal wall. A few extended in a superior direction to lie anterior to the common iliac vessels. None extended higher than the bifurcation of the aorta, a point that often marked the superior margin of the dissection at lymphadenectomy. A few lymphoceles reached into the paravaginal spaces where they could be palpated on vaginal examination. We have demonstrated indentation of the bladder filled with radiopaque material.

Usually the fluid extracted was a thin, yellowish liquid, but some was gray and almost colorless. One patient had a thin, brown liquid on vaginal wall aspiration and 4 days later on abdominal drainage it was found that the lymphocele contents had been changed by bacterial contamination to a cream-colored, thick fluid. One lymphocele cavity was completely filled by a gray gel; another had a mixture of a thin, gray fluid and a gray gel.

No bacteriologic studies were done on the contents of one lymphocele and in 3 cases no attempt was made to drain the lymphoceles. A smear and culture were made in the remainder of the cases and results were positive in 8 cases. Gram-positive cocci and a variety of positive cultures were reported. Since the collection of fluid did not have the physical appearance of an infection except in one case obviously infected by an earlier vaginal aspiration, the culture growth was probably a contamination.

Usually the walls of the cavity have been coated with a gray material 1 to 2 mm. in thickness presumably formed by precipitation of solids from the lymphocele fluid. Some of these linings have been thick enough to resemble the walls of a cyst and pieces could be peeled away for histologic study. One wall was described as a "dense network of fibrin with many enmeshed lymphocytes—no endothelial lining present." Another was "portions of an amorphous eosinophilic granular material containing necrotic cells having clear cytoplasm. Diagnosis, amorphous debris."

Six of the lymphoceles occurred on the left side, 3 on the right, and 3 bilaterally.

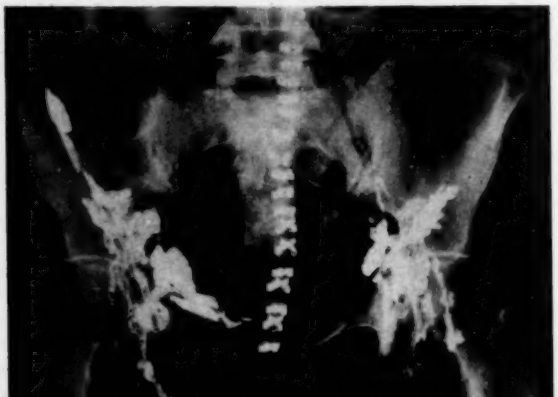

Fig. 1. Direct lymphogram by cannulation of lymph channel in dorsum of each foot; 24 hours after radical cervicectomy and lymphadenectomy. Pooling of the radiopaque agent (Ethiodol) in retroperitoneal space and spread into one femoral canal. Deep pelvic nodes and lymphatic pathways have been removed. Abdominal nodes do not fill because afferent vessels removed.

Time of appearance of lymphocele. The follow-up on our 95 lymphadenectomies has been excellent. Practically every patient was seen at least every month during the first year after the operation. Because of the frequent examinations, we know with reasonable accuracy how long after the lymphadenectomy the lymphocele appeared. The earliest we discovered a lymphocele after lymphadenectomy was 9 days and the latest 171 days. The average length of time for the 12 patients was 51 days.

The lymphocele made its appearance in two distinct and about equally frequent ways. One type of patient had only the usual amount of postoperative induration in the lateral pelvic region and over a short period of time was found to have developed a lymphocele. The second type of patient was the patient who had a massive induration in the lateral pelvic space and this induration was slowly replaced by a lymphocele. All of the women with massive indurations did not develop a lymphocele but had a gradual disappearance of the induration.

The length of hospitalization and the complications after lymphadenectomy were not different when the women with and without lymphocele were compared.

Symptoms. Some of the patients with a lymphocele were unaware of its presence because it caused no localized symptoms. A few noticed a swelling above the inguinal ligament and in adjacent soft parts of the lower extremity. This swelling was described more as a stiffness rather than an actual pain. Four patients had edema involving most of a lower extremity. One woman had a marked edema of the vulva which persisted for several months. Minor degrees of vulval edema may have gone unnoticed.

Our lymphoceles did not affect the peripheral pulses.

The most common complication of the lymphocele and the one that usually led to prompt diagnosis and eventual surgical treatment of the lymphocele was urinary tract infection. Seven of the 12 patients had to be admitted to the hospital because of pyelonephritis. Excretory urograms were done promptly and, although only two

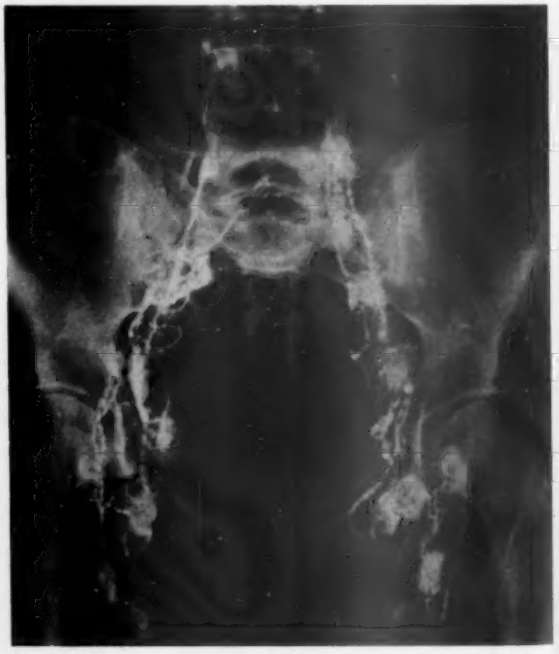

Fig. 2. Typical direct lymphogram before operation. Superficial and deep pelvic nodes. Lymphatic pathways to abdominal nodes.

showed any degree of ureteral obstruction, all had at least a minor degree of ureteral dilatation and hydronephrosis. The pyelonephritis usually responded rapidly to the indicated antimicrobic agent. When the pyelonephritis did not improve rapidly, surgical drainage of the lymphocele was performed with satisfactory effect on the infection.

The full responsibility for the urinary ectasis cannot be placed on the lymphocele. Routine films after the lymphadenectomy operation, even those without radical hysterectomy or other dissection of the ureters, consistently showed some dilatation of both ureters, and this, at least in some instances, persisted without symptoms for weeks.

Our lymphoceles have not produced any permanent disability and have not adversely affected the disease that necessitated lymphadenectomy. All patients are alive and well.

Cause of lymphoceles

It is generally accepted that the division of afferent lymphatic channels during lymphadenectomy initiates the formation of lymphoceles. At least under certain circumstances, lymph continues to flow through these vessels and becomes trapped in retroperitoneal spaces. This concept is supported by Fig. 1. This is a film made by direct lymphography* 24 hours after a radical abdominal cervicectomy and pelvic lymphadenectomy. The radiopaque agent can be seen pooling in the lateral retroperitoneal spaces. The location of this pool is the usual location for lymphoceles. A film taken one month later showed no real difference in the amount and location of the radiopaque medium. Pelvic nodes are not seen in Fig. 1 because they have been removed by the lymphadenectomy. The nodes seen in the illustration have been proved by stereoroentgenograms to be superficial inguinal and femoral nodes. This film was taken 30 minutes after injection into a cannulated lymph channel in the dorsum of the foot.

Fig. 3. Lateral film of same postlymphadenectomy patient as in Fig. 1. Some tendency of the radiopaque agent to collect in anterior part of retroperitoneal space can be seen. Arrows indicate radiopaque material deep in pelvis.

Lymphograms of patients who have not had a lymphadenectomy demonstrate the radiopaque medium does not reach this region as rapidly as was noted in Fig. 1, suggesting that the removal of pelvic afferent lymph channels and nodes has reduced the resistance to the flow of lymph.

Also in Fig. 1, and in a 24 hour film of the same patient, the pelvic and abdominal lymph chain is not seen because the lymphadenectomy has removed the afferent vessels to the abdominal nodes.

For comparison, Fig. 2 shows a typical

*This is from an unpublished investigation by Dr. Manuel Viamonte of the Department of Radiology and Drs. Hervy E. Averette, Jr., and Richard C. Hudson of the Department of Obstetrics-Gynecology. The medium used was Ethiodol (E. Fougera & Company, Inc.).

lymphogram in a woman who has not had a lymphadenectomy.

Fig. 3 is a lateral lymphogram of the patient in Fig. 1, taken 24 hours after lymphadenectomy, and shows a rather constant tendency for the pool of lymph to collect in the anterior aspect of the lateral retroperitoneal spaces in front of the external iliac vessels.

One explanation why lymphoceles do not follow all lymphadenectomies may be that the lymph escapes into the peritoneal cavity and is reabsorbed. In our postlymphadenectomy lymphograms, we have observed opaque material that has entered the peritoneal cavity, apparently through openings in the peritonization.

A number of clinical observations have supported the impression that large amounts of lymph are lost into the retroperitoneal space after lymphadenectomy:

1. We do blood volume determinations before lymphadenectomy. This is repeated on the first postoperative day and frequently shows a surprising plasma deficit. The administration of plasma corrects the tachycardia many of these patients have as well as the plasma loss. Riva[7] also corrected this tachycardia with plasma.

2. When the vaginal cuff is open and the retroperitoneal spaces can drain freely after a radical hysterectomy and lymphadenectomy, the quantity of the serous drainage is often surprisingly large.

3. Riva has utilized extraperitoneal suction drainage after extraperitoneal lymphadenectomy and obtained at least 200 ml. from each side in the first 24 postoperative hours.

4. One patient of ours had an abdominal exploration a few days after lymphadenectomy because of a wound separation. Several hundred milliliters of plasma were found in the peritoneal cavity.

A number of factors have been proposed as abetting the formation of lymphocele after lymphadenectomy. Mori suggested that radiation may have been a provoking factor, but he could not prove this hypothesis because his number of irradiated patients was too small. All of Gray's patients and most of Rutledege's patients had radiation therapy before lymphadenectomy but these authors lacked the control patients necessary to prove the radiation was responsible. We are not able to draw a conclusion on the effect of radiation in the University of Miami cases.

Rutledge found that when positive nodes were obtained there was an increase in the incidence of lymphoceles. The nodes were negative in all 12 of our cases. Conversely, no one has been able to demonstrate that the clinical stage of the carcinoma influences formation of lymphoceles. All of our 12 cases were clinical Stage I.

Three patients in our Series A also had a cesarean section with the lymphadenectomy. Two developed lymphoceles, suggesting pregnancy may encourage lymphocele formation. Another patient had a lymphadenectomy 2 weeks after cesarean section but no lymphocele resulted. There were no cesarean sections in our Series B group.

There is a wide acceptance of the idea that lymphocele formation may be increased as lymphadenectomy becomes more radical. Mori believes this is true. If lymphadenectomy, paralleling all pelvic operations, has become more extensive, this change could explain the recent appearance of the lymphocele in gynecologic history.

Our own experience suggests that the thoroughness of the lymphatic dissection influences lymphocele formation. We do not believe that a thoroughness in the technique of lymphadenectomy can be the entire explanation for lymphoceles. Certainly operators with few or no lymphoceles will rightly protest the implication that their lymphadenectomies are less than complete.

Treatment of lymphocele

Lymphoceles can disappear spontaneously. Probably all lymphoceles will disappear if given enough time. Some of our lymphoceles have required surgical drainage because of the resistant pyelonephritis they caused. Even when the pyelonephritis responded promptly to medical treatment, we considered it desirable in some cases to remove the lymphocele

contents in order to prevent recurrence of pyelonephritis.

We have observed the spontaneous disappearance of 5 lymphoceles, requiring from 4 to 78 weeks with an average of 25 weeks and a median of 10 weeks. Naturally, these were lymphoceles presenting few or no symptoms. Two of these 5 spontaneously disappearing lymphoceles were present in two different women who had bilateral lymphoceles. Each patient had one symptomatic lymphocele requiring surgical drainage while the second and smaller lymphocele was permitted to regress spontaneously.

We encouraged spontaneous regression of the lymphocele by bed rest in the hospital with 9 of the 12 patients. Two of the 9 patients, each with 2 weeks of hospitalization, improved so much that operative removal of the lymphocele contents was not necessary. The 7 remaining patients were hospitalized for from 2 to 27 days (average 13 days) with little or no improvement in the size of the lymphocele mass.

Bed rest in some cases caused a slight and disputed reduction in the total size of the mass, and presumably due to reduction of the characteristic edema about the lymphocele. Cortisone and buccal streptokinase-streptodornase were used in some cases without any apparent benefit. The coating of the wall of the lymphocele found in some cases seemed to reduce the possibility of any escape of the encysted fluid.

Rutledge's observations on the refilling of aspirated lymphoceles, the disappearance of radiopaque material injected into the lymphocele and the appearance in the lymphocele of dye injected into the lower extremity demonstrated an equilibrium between the entrapped fluid and the rest of the body. However, these exchanges may not be possible in all lymphoceles, especially in ones of longer duration or those which have formed a pseudocyst wall. The lymphograms we plan to do in the study of future lymphoceles should add to our understanding of the dynamics of the lymphocele fluid.

Needle aspiration of the lymphocele through the abdominal wall should be possible when the contents are liquid. We have not attempted it. The irregular shape of some cavities we have opened indicates that complete removal of the fluid usually would be impossible. Injury to the external iliac vessels would be an associated risk and infection from abdominal taps have been reported.

A needle can easily be inserted when the lymphocele extends into the paravaginal region. At least in multiparas with a redundant vaginal mucosa a lymphocele presents as a convenient bulge. With a woman in the lithotomy position the paravaginal portion of the lymphocele is the dependent part and aspiration should be more complete than when it is done through the abdominal wall.

We have used vaginal wall aspiration in 2 women. Twelve days after cesarean section and lymphadenectomy the first patient was placed in the lithotomy position preparatory to the institution of intracavitary radiation. Tremendous bulging of redundant vaginal walls by lymphoceles prevented exposure of the cervix. Lymphoceles in this patient had not been recognized prior to this procedure. Lymphocele fluid was removed from each side. The lymphoceles did not reappear.

The second patient with vaginal aspiration of a lymphocele had a unilateral mass and 700 ml. of a thin, brown fluid was removed. When a small amount of fluid remained and was being removed too slowly, the needle was replaced by a 19 gauge catheter. Drainage continued slowly through this catheter for only a few hours and then it became irrevocably plugged. Because the lymphocele appeared incompletely emptied, an abdominal drainage was performed 4 days later. This time 500 ml. of a heavy, cream-colored fluid, evidently changed by the contamination of the vaginal procedure, was obtained. Culture of this fluid grew *Staphylococcus aureus,* coagulase positive.

Abdominal surgical drainage of the lymphoceles was necessary in 8 of the 12 patients (one patient was cured by vaginal aspiration and 3 had a spontaneous regression of the

lymphocele). The surgical approach to the lymphocele was the same as the one we utilized for extraperitoneal lymphadenectomy. An adequate incision parallel to the inguinal ligament is made. Beginning at the external inguinal ring, the external ring, the external oblique fascia, internal oblique muscle, and transversalis are divided under the skin incision. The inferior epigastric vessels are incised between ties. The peritoneum often is very adherent from the reaction to the lymphadenectomy, but it can be dissected in a medial direction from the pelvic wall, unroofing the lymphocele. The lymphocele contents are aspirated. Soft rubber Penrose drains are used to drain the extremities of the cavity. On two occasions the lymphocele was too shallow for rubber drains to be practical and the cavities were lightly packed with plain ¼ inch gauze. The wound was lightly closed in layers, permitting an adequate space around the drains. Drains were removed from 5 to 10 days, depending on the duration of the drainage. Usually the draining fluid became infected but there were no serious wound infections.

The postoperative course of the patients was uncomplicated and the lymphocele cured except in one case. This patient, 2 months after abdominal drainage, had a recurrence of the lymphocele, possibly because the wound had been closed too tightly. Exploration of the same site was necessary. The tissues were extraordinarily edemous and friable. The trauma of the exploration and the tight packing required interfered with the circulation and a thrombus formed in the external iliac artery. A portion of this artery was replaced by a graft. Now one year after the last operation the patient is completely well.

Prevention of lymphoceles. The successful tying off of lymphatic channels at the periphery of the dissection should prevent lymphoceles, if our concept of the cause of this collection of fluid is correct. Yagi[8] believes that tying off the lymphatic chain at the top and bottom of the dissection has been beneficial. We have tied the superior end of the dissection of the aortic chain, primarily to control bleeding, but it apparently has not helped prevent lymphoceles. The tying of the afferent lymphatic channels at the inferior end of the dissection should be helpful.

Our lymphograms, made by cannulation of a lymph channel in the foot, demonstrate that the channels from the lower extremity enter the retroperitoneal space near the femoral vessels (Fig. 2) and possibly could be completely occluded. We are exploring a technique of mixing a dye with a radiopaque material to help identify these vessels at lymphadenectomy. The contribution that other lymphatic chains may make to the lymphocele formation has not yet been similarly demonstrated.

Riva credits his ligation of lymphatic channels at the femoral canal, the obturator foramen, and the superior portion of the dissection for his having no difficulty with lymphoceles.

Both Gray and Rutledge found that drains placed in the dissection site at lymphadenectomy increased instead of deterred lymphocele formation.

Suction drainage of the retroperitoneal space has been considered helpful by Riva and Symmonds and Pratt.[9]

The open vaginal cuff, when a hysterectomy is performed at the same time as the lymphadenectomy, would be expected to reduce the tendency to lymphocele formation, but obviously gives inconsistent results. Our Series B had a much lower incidence of lymphoceles possibly because a number of these cases had such a vaginal egress for the lymph.

We attempted to prevent lymphoceles by leaving large openings during reperitonization of the pelvic floor but, at least in some cases, this did not succeed. It was hoped that the lymphatic fluid would enter the peritoneal cavity and be reabsorbed. A technique for ensuring the survival of the communication between the retroperitoneal and intraperitoneal spaces might be profitable.

No one has exhibited any influence on lymphocele formation by a preference for

either the extraperitoneal or the transperitoneal approach to lymphadenectomy.

Summary

Following 95 lymphadenectomies 12 patients (13 per cent) with lymphoceles are described. A constant location of the collection of fluid is anterior to the external iliac vessels.

Seven of the 12 patients had pyelonephritis, presumably induced by the presence of a lymphocele.

Lymphoceles appear to be produced by a flow of lymph from divided afferent lymphatic channels and containment of that fluid in a closed retroperitoneal space.

Lymphoceles can disappear spontaneously, but some will require surgical drainage.

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Discussion

Dr. Roy T. Parker, Durham, North Carolina. A more specific and detailed bacteriologic report on the lymphoceles that developed in the early postoperative period would have been of interest since no one writing on this subject adequately differentiates between an extraperitoneal pelvic abscess and an "infected" lymphocele.

The perplexing feature of "lymphocele" or "lymphocyst" is the great variation in the frequency of diagnosis and assignment of symptoms to this condition. Rarely has it been mentioned as a complication of radical Wertheim hysterectomy and pelvic lymphadenectomy in the American literature. Mori and others in the Japanese literature have reported an incidence of approximately 50 per cent after the Okabayashi operation. They have devised special trocar paracoccygeal drains to reduce the morbidity of this complication.

From 1944 through 1960 we have performed approximately 320 radical Wertheim hysterectomies and radical pelvic lymphadenectomies in the treatment of cervical cancer. Lymphocele has been diagnosed in only 4 patients, and only one patient has required surgical drainage. Always, we have left the cuff wide open, and we usually employ drains for 3 to 5 days. The copious drainage noted must be attributed to serum loss from the large area of raw pelvis as well as lymph. Hematoma formation is not uncommon. Infection with localized pockets of pus develop and must be drained. Urinary and rectal fistulas develop and drain through the vaginal cuff. All of these we have encountered and we consider them problems but not lymphoceles.

In pelvic lymphadenectomy without hysterectomy the "closed space," without egress for blood, serum, and lymph, should predispose to reservoirs of fluid. Even here there is a great discrepancy as to frequency of occurrence. It does not seem reasonable to attribute pelvic cellulitis, abscess formation, leg edema, and obstructive uropathy to lymphocele formation.

In extraperitoneal pelvic lymphadenectomy, constant sump drainage with suction, for as many days as there is an extravasation of fluid, has proved helpful. The drains are then removed and the sinuses kept open by daily probing. This measure will promote primary wound healing and less frequent lymphoceles.

Dr. Frank R. Lock, Winston-Salem, North Carolina. Dr. Ferguson quoted us as having had a 5 per cent incidence of lymphocele, but I need to point out this is not the gross incidence of lymphocele encountered, but represents the ones that we consider significant. It was, in fact, only in the past year or 18 months, after the initial reports were made on this problem, that we began to appreciate its frequency.

I believe we have had 2 deaths which can be attributed to the complication. One of them resulted from complications with a massive lymphocele; the other may have been due to the uncontrollable loss of lymph causing reduced plasma volume and electrolyte imbalance. Although this lesion is one that usually is not a serious complication, we must appreciate that it represents an unfamiliar field of physiology and anatomy. How does the lymphatic circulation affect the metabolism of electrolytes, protein, and other lymph fluid components?

The patient in whom death can be definitely attributed to lymphocele developed a huge fluctuant pelvic mass that extended to the umbilicus. We did not recognize it initially and approached this by aspiration of over a liter of fluid on several successive days. The patient was seriously embarrassed by the massive accumulation and a decision was made to attempt surgical drainage. This was followed by continuous profuse loss of lymph, secondary infection, progressive deterioration, and death. The complication followed radical hysterectomy with lymphadenectomy in a patient who had had high intensity radiation. Inspection of the lymphocele cavity 2 months postoperatively did not show the wall to which Dr. Ferguson refers. We have observed this, but in this patient the vessels, nerves, and pelvic structures appeared much as they had at the time we closed the basic operation.

Dr. Ferguson (Closing). Dr. Parker asks a very provocative question when he inquires how lymph node dissections can have different degrees of radicalism. To assist in answering this question please recall that I have divided our 95 lymphadenectomies into two groups, Series A and Series B. The patients in Series B (patients with lymphadenectomy plus another procedure) had a "less radical" lymphadenectomy.

With patients scheduled for lymphadenectomy only there is the time and the inclination to do a more complete job. A vessel may have removed from it only the readily visible lymph nodes and the tissue on the more accessible interior surface or, on the other hand, the entire circumference of the same vessel may be completely stripped of all areolar and lymphatic tissue. There can be a difference in the depth to which you follow the external iliac vessels as they begin to disappear into the lower extremity and a difference in the thoroughness of denudation of the inferior branches. Given a greater amount of time, every operator can remove more tissue from the obturator fossa. With more time the operator can work higher and more carefully on the vena cava and the aorta.

The preoperative differentiation between lymphocele and pelvic abscess became easier as we gained experience with the lymphocele. The fever that most of these women had on readmission to the hospital was clearly due to pyelonephritis. The history and physical examination were characteristic of pyelonephritis. Excretory urograms showed a greater dilatation of the ureter and renal pelvis on the side of the lymphocele. Microscopic and bacteriologic examination of the urine supported the diagnosis of pyelonephritis. The improvement in the febrile state of the patient paralleled the response to the treatment we directed toward the organism found in the urine. The appearance of the mass was not characteristic of an abscess. There was edema of the surrounding tissue but tenderness was either minor or absent. There was no reddening of the skin over the mass. The fluid in the lymphocele did not look like pus and the smears and cultures made from the fluid were not characteristic of an abscess.

OBSTETRICS

A comparative study of the alkali reserves of maternal and fetal blood

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IN A recent report from this laboratory[12] the alkali reserve of women in the course of pregnancy was reported as ranging between 20.5 and 24.0 mM. per liter, with a mean of 22.2 mM. per liter. The value for the alkali reserve reported represented the total carbon dioxide concentration of the blood plasma at a carbon dioxide tension of 40.0 mm. Hg with the blood hemoglobin fully oxygenated. Some of the experimental and interpretative pitfalls of other definitions of "alkali reserve" were commented on in that report.

As part of our interest in the study of the exchange of the respiratory gases across the placenta and of the effect of acid-base balance upon it, we have proceeded to study the alkali reserve of the blood of pregnant women and their infants. The data thus obtained form the substance of this report.

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***Student Research Fellow, Josiah Macy, Jr., Foundation, 1959-1960; Henry Strong Denison Scholar, 1960-1961.*

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Materials and methods

Blood from 12 women and their infants was used for these determinations. The experimental and mathematical methods of obtaining the alkali reserve of these samples of blood are extensively described in the previous report from this laboratory.[12]

In obtaining the samples of blood from the maternal antecubital vein a size 16 needle was used which was placed in position 15 minutes prior to the obtaining of the sample, so that no stasis occurred at the time of sampling. The needle was kept patent by means of a solution of 5 per cent dextrose in water, care being taken that the intravenous drip did not proceed at a rate greater than 6 drops per minute. This was done to obviate the known effects of hypotonic expansion of maternal extracellular fluid volume upon the fetus.[3]

Immediately upon delivery, and by means of a three-way stopcock, the first 5 c.c. of maternal blood was discarded and the re-

Table I. Data obtained from cesarean section prior to labor

1 Case No.		2 pCO_2	3 Total CO_2	4 CO_{2_p}	5 Uncorrected $BHCO_3$	6 Corrected $BHCO_3$	7 Corrected total CO_2	8 pH	9 pH at pCO_2 40 mm. Hg	10 Alkali reserve
1	M	35.49	17.79	1.07	16.72	18.58	19.65	7.34	7.308	20.55
	M	42.32	19.19	1.27	17.92	19.90	21.17	7.30		
	F	39.23	18.25	1.18	17.07	18.96	20.14	7.31	7.302	20.30
	F	47.15	20.22	1.42	18.80	20.89	22.31	7.27		
2	M	33.55	18.57	1.01	17.56	19.51	20.52	7.39	7.335	21.82
	M	43.10	20.33	1.30	19.03	21.14	22.44	7.31		
	F	34.59	17.93	1.04	16.89	19.71	20.75	7.38	7.334	21.75
	F	44.31	19.60	1.33	18.27	21.32	22.65	7.30		
3	M	34.97	16.58	1.05	15.53	18.99	20.04	7.36	7.315	20.90
	M	44.14	18.05	1.33	16.72	20.44	21.77	7.29		
	F	36.26	18.69	1.09	17.60	19.55	19.64	7.35	7.312	20.73
	F	45.47	20.28	1.37	18.91	21.01	22.38	7.29		
4	M	36.28	20.72	1.09	19.63	21.81	22.90	7.40	7.363	23.18
	M	43.44	21.23	1.30	19.92	22.13	23.43	7.33		
	F	35.14	20.42	1.06	19.36	21.51	22.57	7.41	7.365	23.30
	F	43.23	21.53	1.30	20.23	22.48	23.78	7.34		
5	M	36.87	18.71	1.11	17.60	19.56	20.67	7.35	7.337	21.90
	M	42.12	20.70	1.27	19.44	21.59	22.86	7.33		
	F	36.91	18.86	1.11	17.75	19.72	20.83	7.35	7.337	21.90
	F	41.94	20.57	1.26	19.31	21.45	22.71	7.33		
6	M	33.28	16.63	1.00	15.63	17.36	18.36	7.34	7.284	19.55
	M	42.46	18.07	1.28	16.79	18.66	19.94	7.26		
	F	33.60	16.42	1.01	15.41	17.12	18.13	7.33	7.280	19.38
	F	44.95	18.48	1.35	17.12	19.03	20.38	7.25		

maining maternal sample then obtained simultaneously with the fetal sample, which was obtained from the umbilical vein.

Results

In Table I we have given the data obtained from 6 patients in whom cesarean section was carried out prior to the onset of labor. In Table II we have given the data obtained in 6 patients in whom the data were obtained at vaginal delivery which followed varying periods of labor.

In each table Column 1 gives the case number and states whether the blood sample was of maternal or fetal origin. Throughout the tables the first two lines give data for maternal blood, and the last two lines data for fetal blood. Column 2 gives the carbon dioxide tension, in millimeters of mercury, with which the individual blood samples were equilibrated. Column 3 gives the total carbon dioxide concentration in the samples of blood, uncorrected for the one part in ten of anticoagulant which was a 2 per cent $K_2C_2O_4$—0.6 per cent NH_4F mixture. Column 4 gives the carbon dioxide physically dissolved in the blood-anticoagulant mixture. Column 5 gives the bicarbonate concentration of the sample, uncorrected for the anticoagulant. Column 6 gives the bicarbonate concentration of the sample corrected for the anticoagulant. Column 7 gives the total carbon dioxide concentration, corrected for the anticoagulant. Column 8 gives the pH, calculated by use of the Henderson-Hasselbalch equation, using the PCO_2 and the corrected bicarbonate given in Columns 2 and 6, respectively. Column 9 gives the pH of the blood at a carbon dioxide tension of 40 mm. Hg in the presence of the alkali reserve for the particular sample, which figure is given in Column 10.

It will be noted that in all the samples obtained at cesarean section prior to the onset of labor the alkali reserves of the maternal and fetal blood were very similar. It will also

Table II. Data obtained from vaginal deliveries

1 Case No.		2 pCO_2	3 Total CO_2	4 CO_{2_d}	5 Uncorrected $BHCO_3$	6 Corrected $BHCO_3$	7 Corrected total CO_2	8 pH	9 pH at pCO_2 40 mm. Hg	10 Alkali reserve
7	M	37.26	16.18	1.12	15.06	16.73	17.85	7.27	7.253	18.28
	M	46.11	17.38	1.39	15.99	17.75	19.14	7.21		
	F	37.47	15.86	1.13	14.73	16.37	17.50	7.26	7.250	18.15
	F	43.53	17.32	1.31	16.01	17.79	19.10	7.23		
8	M	33.67	13.58	1.01	12.57	13.95	14.96	7.24	7.196	16.15
	M	42.77	15.20	1.29	13.91	15.44	16.73	7.18		
	F	33.45	16.89	1.01	15.88	17.63	18.64	7.34	7.292	19.88
	F	41.27	18.28	1.24	17.04	18.91	20.15	7.28		
9	M	37.45	14.56	1.13	13.43	14.91	16.04	7.22	7.203	16.41
	M	48.60	16.24	1.46	14.78	16.41	17.87	7.15		
	F	39.54	14.85	1.19	13.66	15.16	16.35	7.21	7.203	16.39
	F	42.06	15.14	1.27	13.87	15.40	16.67	7.18		
10	M	33.84	13.47	1.02	12.45	13.82	14.84	7.23	7.210	16.64
	M	41.63	15.56	1.25	14.31	15.88	17.13	7.20		
	F	35.57	14.17	1.07	13.10	14.54	15.61	7.23	7.208	16.56
	F	44.23	15.83	1.33	14.50	16.10	17.43	7.18		
11	M	35.42	15.86	1.07	14.78	16.41	17.48	7.29	7.277	19.24
	M	44.78	19.10	1.35	17.75	19.70	21.05	7.26		
	F	35.74	18.70	1.08	17.61	19.81	20.88	7.36	7.353	22.70
	F	43.14	21.51	1.30	20.21	22.73	24.03	7.34		
12	M	31.09	17.26	0.94	16.32	18.12	19.06	7.39	7.321	21.16
	M	44.55	20.01	1.34	18.67	20.72	22.06	7.29		
	F	34.47	18.21	1.04	17.17	19.06	20.10	7.36	7.319	21.07
	F	46.64	20.15	1.40	18.75	20.81	22.21	7.27		

be noted that in these maternal samples the alkali reserve was not different from that reported for women in the course of pregnancy.[12]

From Table II it will be apparent that once labor has ensued the alkali reserve of the maternal blood tends to decrease, presumably as a result of fixed acids produced by the laboring uterus. In Cases 7, 9, 10, and 12, the fetal alkali reserve is found to be about the same as that of the mother, but in Cases 7, 9, and 10 it will be seen that this similarity in alkali reserves occurs at a lower level than exists in the group prior to the onset of labor. In Cases 8 and 11 the fetal alkali reserve has by no means reached similar levels with that of the maternal blood, and in fact shows values much more representative of those obtained from mothers and fetuses prior to the onset of labor. In Figs. 1 and 2 we have graphically represented all of the points obtained experimentally, thus showing more clearly that the subject matter presented consists of carbon dioxide dissociation curves, constructed with fully oxygenated blood, between the limits of carbon dioxide tensions used for the purpose of these experiments.

Comment

The relative position of the maternal and fetal carbon dioxide dissociation curves with respect to each other has been a subject of confusion for many years. That some of this confusion might be due to the experimental circumstances under which the blood samples, used to construct these dissociation curves, were obtained was first clearly implied in the data of Barron,[2] obtained with the blood of sheep. Commenting on Keys'[10] observation that the alkali reserve of fetal blood samples after cesarean section was higher than that of maternal blood obtained after the delivery of the fetus, Barron confirmed this finding, provided the blood samples were drawn under similar circumstances, after the

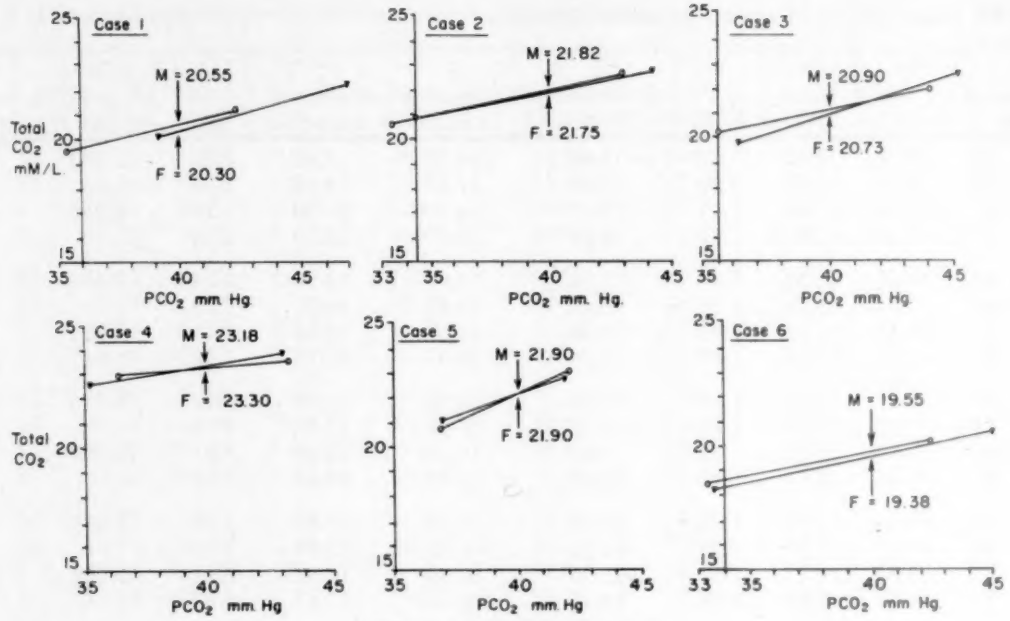

Fig. 1. Cesarean sections.

lambs had been delivered by cesarean section. In the course of further experiments, however, he noticed that the alkali reserve of the blood plasma as sampled 15 to 20 minutes after the ewe was anesthetized and restrained was between 2.5 and 10.7 volumes per cent less than that of a first blood sample, obtained prior to the anesthesia and restraining. In a series of experiments in which the alkali reserve was determined prior to anesthesia, after anesthesia at delivery, and in the fetal blood at delivery, he noticed that the closest approximation between maternal and fetal alkali reserves was produced in those cases in which the alkali reserve of the maternal blood had least changed in the course of the procedure carried out to obtain the maternal and fetal samples. These data prompted us to compare maternal and fetal alkali reserves in cases prior to the onset of labor and at the time of vaginal delivery. As will be seen from the data obtained at cesarean section prior to the onset of labor, the observations of Barron find ample confirmation since remarkably similar alkali reserves are found to exist in maternal and fetal blood when the alkali reserve of the maternal blood is not different from that found previously in this laboratory[12] to exist in the blood of women during the course of pregnancy. Similarly, in Case 12, from the vaginal delivery series, in which the maternal alkali reserve was the same as that which would be found in a woman in the course of normal pregnancy, the maternal and fetal alkali reserves were identical.

Once labor ensues, the effect of fixed acids produced in the course of labor are brought to bear on the alkali reserve of the maternal blood. Thus it is seen that the alkali reserves of these women were markedly lowered. The behavior of the fetal alkali reserve under such circumstances follows an unpredictable pattern. In Cases 7, 9, 10, and 12 the alkali reserves were found to be similar, but in Cases 7, 9, and 10 this similarity occurred at a considerably lower level of alkali reserve than exists in the cesarean section group. In Cases 8 and 11 it is seen that a considerable difference in alkali reserves exists, the fetal value being the higher, and therefore these cases resemble the circumstances described by Keys in goats. The ultimate, remarkable, similarity between the alkali reserves, although at considerably lower levels, need not necessarily be taken to mean that equilibration of bicarbonate between the maternal and fetal compartments has occurred as such, or across the placenta. Recently, Blechner, Meschia, and Barron[5]

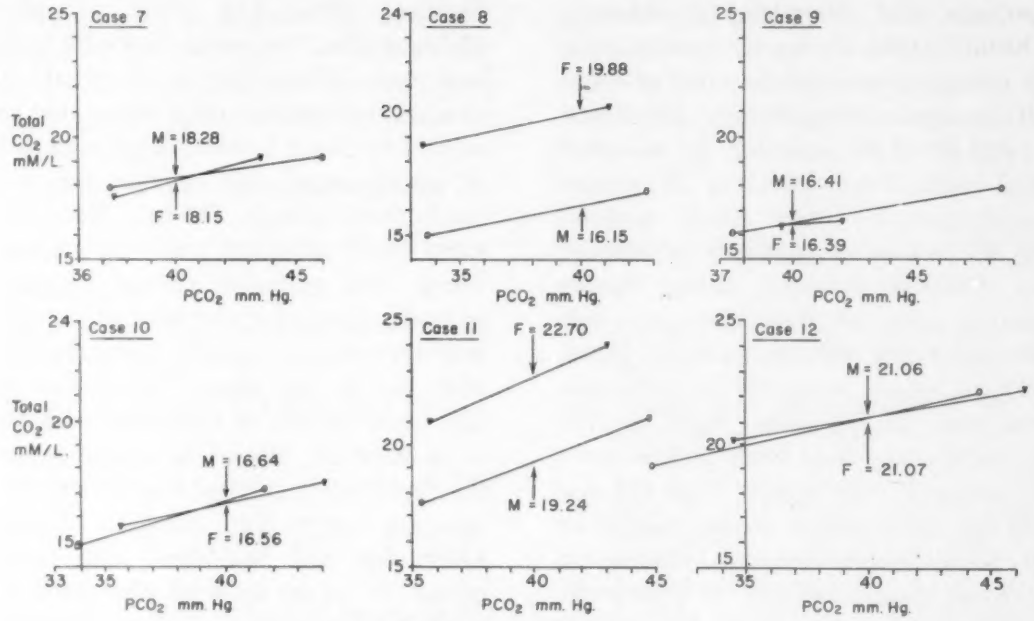

Fig. 2. Vaginal deliveries.

have shown that the difference between the carbon dioxide tensions on the two sides of the placenta tends to remain fairly constant despite wide variations in the maternal carbon dioxide tension. Nor was there any obvious correlation between the carbon dioxide tension gradient and the pH of either the maternal or the fetal blood. They demonstrated that though differences between concentrations of bicarbonate across the placenta may not be large, the concentration in the fetal blood may be higher or lower than in the maternal, and may remain so for hours. The data clearly demonstrated a degree of independence of these two concentrations, by means of experiments in which marked reductions in maternal plasma bicarbonate concentration, produced by intravenous infusion of NH_4Cl, were not followed by any change in the concentration of bicarbonate in the fetal plasma. They were inclined to ascribe the relative independence of the bicarbonate concentration in the fetal plasma to a limitation in the transplacental exchange of bicarbonate and chloride ions. The similarity of the fetal and maternal alkali reserves of the unanesthetized sheep as shown by Barron and our present data are therefore left unexplained and again raise the question of whether some factor or factors other than direct bicarbonate transfer across the placenta determine the similarity of the bicarbonate levels on the two sides of the placenta.

With this background it is perhaps easier to explain differences in carbon dioxide dissociation curves hitherto published in the literature. Eastman, Geiling, and DeLawder,[7] at PCO_2 40 mm. Hg, report the maternal blood carbon dioxide content at 41 volumes per cent and the fetal as 34 to 38 volumes per cent (18.4 mM. per liter and 15.3 to 17.0 mM. per liter, respectively). Both the maternal and fetal values were however corrected for unsaturation of the hemoglobin with oxygen, so that fully oxygenated blood was not used. In a recent report from this laboratory[9] we have shown that the Bohr effect on maternal and fetal blood was different, so that the Haldane effect, which the above correction for unsaturation of the oxygen represents, must be different for maternal and fetal blood—a fact which Eastman and his co-workers recognized, but which makes comparison with our data impossible. The presence of the fetal carbon dioxide dissociation curve below that of the mother was felt by these workers to facilitate placental transfer of carbon dioxide.

Haselhorst and Stromberger,[8] obtaining their blood samples at cesarean section under spinal anesthesia prior to the onset of labor, placed the fetal carbon dioxide dissociation curve slightly above that for the maternal blood at levels of approximately 50 volumes per cent, therefore more closely approximating the values we obtained at cesarean section. Although the fetal carbon dioxide dissociation curve in their data was only slightly above that for the maternal blood, the PO_2 at which these curves were constructed was 40 mm. Hg. Since at this oxygen tension the fetal blood will be more highly saturated with oxygen than the maternal,[9] this difference in oxygen saturation should have brought the two dissociation curves more closely together, or conversely, with full oxygen saturation the carbon dioxide dissociation curves would have been further apart than they have been reported.

Leibson, Likhnitzky, and Sax,[11] obtaining their blood samples at vaginal delivery, showed a maternal and fetal alkali reserve of 16.2 mM. per liter, and showed them to be identical. Their data therefore correspond well with those in our series studied at vaginal delivery in whom a recurrence of the similarity in alkali reserves occurred, but at much lower levels than are found in the blood of mothers and infants prior to the onset of labor.

Darling and associates[6] found the alkali reserve of fetal blood to be markedly lowered, and that of the pregnant woman moderately so. From this statement Barcroft[1] deduced that the alkali reserve of the fetus was less than that of the mother. They found the mean carbon dioxide content of maternal blood at 40 mm. Hg PCO_2 to be 42.92 volumes per cent and that of the fetus 35.09 volumes per cent, but they corrected their values to "normal lactate." The fetal blood samples came from the umbilical cords of infants delivered vaginally, the blood in each case being obtained within 15 minutes of tying off the cord. Again, therefore, it is difficult to compare these data with those in the present report.

Bartels,[4] also taking into account the Haldane effect and using an identical Haldane effect correction factor for maternal and fetal blood, places the fetal carbon dioxide dissociation curve below that of the mother by about 5 volumes per cent at levels of approximately 40 volumes per cent of total carbon dioxide. The fetal blood samples came from umbilical cords at vaginal delivery. The maternal carbon dioxide dissociation curve for purposes of comparison was an average one for pregnant women after Rossier and Hotz.[13] These data therefore again cannot be compared with ours.

In summary, it will be apparent that of the previously published carbon dioxide dissociation curves only the data of Leibson, Likhnitzky, and Sax agree with those reported by us in some of our cases in the vaginal delivery group. It is our feeling that in the normal undisturbed preparation the alkali reserves of maternal and fetal blood are very similar and provide some gauge of the stability of the biological preparation under study. By the same token, it must be apparent that the Haldane effect, tending to alter the position of these two carbon dioxide dissociation curves relative to one another, must have a not inconsiderable effect on the exchange of carbon dioxide between maternal and fetal blood. Since these Haldane effects are different for maternal and fetal blood, a reassessment of some of the aspects of carbon dioxide transfer from the fetus to the mother must await quantitation of this difference. Such data will form the substance of a future report.

Summary and conclusions

1. The alkali reserves of maternal and fetal blood have been compared in a group of women and their infants at cesarean section prior to the onset of labor, and at vaginal delivery.

2. When the maternal alkali reserve does not differ appreciably from that found in the course of normal pregnancy, the alkali reserves of fetal and maternal blood, as defined, tend to be identical.

3. Labor tends to decrease the maternal alkali reserve.

4. When such a decrease in maternal alkali reserve has occurred, a tendency for the fetal and maternal alkali reserves again to reach similar levels is seen to occur at these lower levels.

5. A time lag may occur between the re-establishment of similar alkali reserves on the two sides of the placental barrier.

6. Carbon dioxide dissociation curves which have previously been reported in the literature are examined in the light of these findings.

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Electrophoretic distribution of proteins in amniotic fluid and in maternal and fetal serum

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SEVERAL articles have appeared in the recent literature on the protein content of human and animal amniotic fluid in relation to fetal or maternal serum.[1, 3, 4, 7, 8, 12] The present study was undertaken to compare the relative distribution of protein fractions in amniotic fluid, taken during the final stage of delivery, with the relative distribution in the corresponding fetal and maternal serum obtained immediately after birth.

Materials and methods

Maternal venous blood, cord blood, and amniotic fluid were collected from 23 healthy women during delivery at term. In 20 women, samples were taken at the time of vaginal delivery and in 3 women under anesthesia during the performance of a cesarean section.

The amniotic fluid was obtained by puncturing the amniotic membrane with a syringe when the cervical opening was at least 3 cm. wide. Care was taken not to include vaginal secretions or blood. In the cases of cesarean section, the fluid was collected by puncture of the membrane following the incision of the uterine wall.

Total protein was determined in the serum and amniotic fluid samples by the biuret method.[11]

The amniotic fluid sample was cleared by centrifugation prior to the determination. For the electrophoretic separation of the fluid proteins, the protein content of the amniotic fluid had to be raised to about 5 per cent. This was achieved through overnight dialysis against 25 per cent solution of polyvinylpyrrolidone at 4° C. followed by dialysis against Veronal buffer pH 8.6, ionic strength 0.1.

Paper electrophoresis was performed according to the method of Köiw, Wallenius, and Grönwall.[5] Samples of maternal and fetal sera as well as the concentrated amniotic fluid were applied on Whatman 3 mm. paper strips and separated simultaneously. The protein-stained strips (amido black) and the lipid-stained strips (oil red O) were scanned in an automatic recorder (Spinco Analytrol). Moving-boundary electrophoresis was performed on several samples in Perkin-Elmer apparatus, Model 38A, equipped with the Philpot-Svennson optical system.

Results

Fig. 1 summarizes the data on electrophoretic distribution of protein fractions in fetal and maternal sera as well as in the

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amniotic fluid. A representative set of 3 paper electropherograms stained for proteins and lipids is given in Fig. 2. Fig. 3 depicts a moving-boundary resolution of amniotic fluid proteins.

As seen from Fig. 1, the total protein values are lowest in amniotic fluid. The relative concentration of albumin in amniotic fluid somewhat exceeds that in the fetal serum and is markedly higher than in maternal serum. The percentages of α- and β-globulin fractions in fetal serum and amniotic fluid are very close, but both are lower when compared with maternal serum. On the other hand, the relative concentration of γ-globulins in the amniotic fluid is markedly lower than in fetal and maternal serum.

It should be pointed out that the α-globulin values given in Fig. 1 pertain to α_2-globulins and that the albumin values in the figure include the α_1-globulin fraction. In maternal and fetal serum, this fraction is readily resolved and comprises between 3 and 7 per cent of the total serum protein. In amniotic fluid, the α_1-globulin fraction appears to account for a somewhat larger proportion of total protein but it follows the albumin zone so closely that it could not be separately determined with sufficient accuracy. For the sake of comparison, the albumin and α_1-globulin content was therefore calculated in all groups as one fraction.

Fig. 2 shows both the protein and lipid distribution pattern in the serum and amniotic fluid from one subject. As is well-known, the concentration of β-lipoproteins in the maternal serum is elevated as compared with that of normal controls and in the newborn considerably decreased, as compared with the mother. It is remarkable however that no protein-bound lipids could be detected in the amniotic fluid even upon fifteenfold concentration. A small spot at the point of application does seem to be caused by some particulate matter, since the almost total absence of lipids in amniotic fluid was also confirmed by chemical determination.[2, 6]

Table I. Ratio of albumin to globulins in aminotic fluid and maternal and fetal serum*

	Maternal serum	*Fetal serum*	*Amniotic fluid*
Albumin/total globulins	0.56	0.90	1.07
Albumin/α- plus β-globulins	0.93	1.76	1.67
Albumin/γ globulins	1.40	1.84	3.00

*Calculated from the mean values given in Fig. 1.

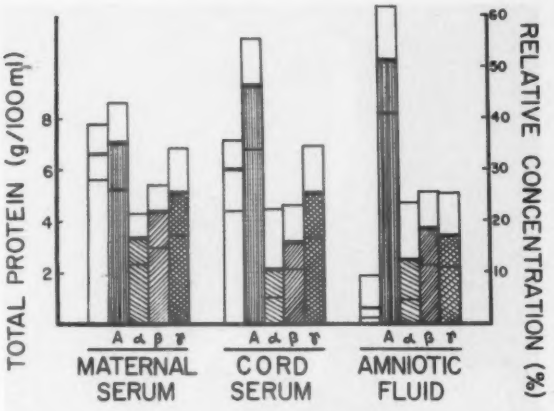

Fig. 1. Total and relative concentrations of protein fractions in maternal and fetal serum and corresponding amniotic fluid. In each column, the mean of 23 determinations is marked by a heavy horizontal bar, the range is indicated by lower and higher thin horizontal lines.

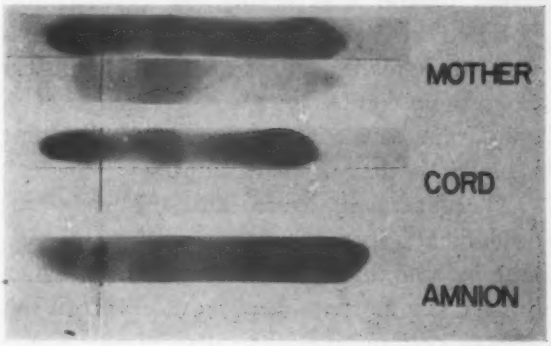

Fig. 2. A set of 3 paper electropherograms. In each group the upper strip was stained with amido black for protein pattern and with oil red O for lipid pattern.

Comment

The results of this study point to a similarity in the electrophoretic pattern of amniotic fluid and fetal serum. On the other hand, larger differences exist in the relative concentrations of protein components when maternal serum and amniotic fluid are com-

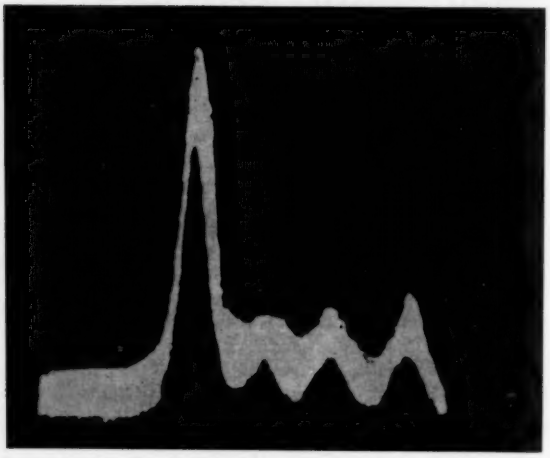

Fig. 3. Representative photograph of the ascending boundary obtained with amniotic fluid in a 2 ml. cell of Perkin-Elmer apparatus in barbital buffer pH 8.6, ionic strength 0.1.

pared. These conclusions are further emphasized in Table I, where arbitrary ratios between relative concentrations of the different protein components were compared. The only fraction showing a somewhat different behavior is that of γ-globulins.

The data available in the literature[1, 3, 4, 7] do indicate that the relative albumin content in amniotic fluid is consistently higher than in the maternal and fetal serum. In the several communications cited, there is less agreement on the relative distribution of the globulin fractions which may be due, at least in part, to the different techniques applied by the investigators. There are only a few reports on comparison of amniotic fluid protein components with the corresponding maternal and fetal serum obtained at the same time,

From the similarities in the protein pattern indicated above, it is tempting to consider the possibility that the fetal circulation supplies proteins to the amniotic fluid. Absence of large protein molecules in the amniotic fluid, such as lipoproteins, fibrinogen, and reduction in γ-globulins clearly indicates that the proteins of the pool, serving as the source of amniotic fluid, undergo sequestration, perhaps by filtration or diffusion. In this respect the amniotic fluid protein appears similar in composition to other interstitial fluids. The sequestered components of amniotic fluid nevertheless show much resemblance in distribution to that of fetal serum. This fact may lend some support to the proposition advanced recently,[9, 10] that the macromolecular components of the amniotic fluid are predominantly derived through transudation from various fetal tissues, rather than by secretion or filtration from maternal circulation.

There remains the problem of the quantitative and qualitative importance of the contribution of various protein pools to the amniotic fluid at different times during pregnancy. Wirtschafter and Williams[12] observed marked changes in the protein content and distribution pattern of rat amniotic fluid at various times during gestation. The albumin content was found to increase markedly only during the last days of gestation. We have an indication that the human amniotic fluid remains fairly constant in composition throughout pregnancy. Several electrophoretic resolutions of protein in fluids obtained at the second, fourth, and sixth months of pregnancy do show that albumin comprises more than 60 per cent of amniotic fluid protein.[2] Further work is currently being performed to investigate this question thoroughly.

Summary

1. Proteins of amniotic fluid were resolved electrophoretically and the results were compared with the resolution of corresponding fetal and maternal serum.

2. The protein distribution in amniotic fluid shows more similarity to that of fetal rather than maternal serum.

3. The possible bearing of these results on the origin of amniotic fluid protein is discussed.

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The maternal-fetal oxygen pressure gradient in spontaneous and oxytocin-induced labors

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THE oxygen pressure gradient may be defined as the difference between the partial pressure of oxygen in the intervillous space of the placenta and that in the umbilical vessels of the fetus. It is directly proportional to the rate of flow of oxygen across the placental barrier.[1]

The aims of this investigation are to study the effect of an oxytocic drug (Pitocin), administered for the induction or stimulation of labor at term, on the state of oxygenation of the newborn infant and to correlate the clinical condition of the infant at birth with the laboratory data. The study was initially conceived with the purpose of either substantiating or refuting, by direct quantitative measurement, the widely held clinical impression that oxytocic drugs diminish fetal oxygenation in utero, and hence play a role in the causation of fetal distress.

Review of previous work

There have been many studies made on the oxygenation of the newborn infant by estimating the oxygen saturation in the umbilical vessels.[3-10] The results obtained from these studies showed wide divergencies, and it is now considered that evaluation of the oxygen status of the newborn without knowledge of the prevailing maternal oxygenation is of limited value.

Later studies attempted to correlate these factors by simultaneous samplings of the maternal and newborn blood streams. Blair-Bell and associates[11] utilized the maternal radial artery and antecubital vein. Subsequently, arterial and venous blood samples were taken from the uterine vessels at cesarean section.[12] Barron and Alexander[13, 15] established the concept of the "oxygen pressure gradient" between the maternal and fetal blood streams of the sheep. McClure-Browne,[16] in his studies of placental blood flow in toxemia of pregnancy, was one of the earliest investigators to tap the human intervillous space.

Prystowsky[1] subsequently tapped the intervillous space under anaerobic conditions and established this method of investigating the oxygen pressure gradient across the placental membrane in the human.

The pharmacological properties of the oxytocic drugs have been extensively studied with particular reference to the contractility of uterine musculature.[17-19] Quantitative measurements of the hydrostatic pressures of amniotic fluid and of the blood in the intervillous space in normal and oxytocin-controlled labors have also been made.[20-23]

There does not appear to have been any previous report in the literature concerning the effect of oxytocic drugs on fetal oxygenation.

On the obstetrical service of the Mount Sinai Hospital, oxytocin administered by intravenous route, usually accompanied by amniotomy, is the most commonly used method of either inducing or stimulating labor. On the private service labor is induced

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in 14.7 per cent of patients and in 10 per cent labor is stimulated; the corresponding figures for the ward service are 2.6 and 6.9 per cent. Antepartum oxytocin is therefore administered to almost 25 per cent of all private and 10 per cent of ward patients.

Technique and materials

We selected as controls patients who had had a normal prenatal course and an uncomplicated labor with a cephalic presentation; moreover, the oxytocin series was similarly made up of normal patients in whom labor had been electively induced or stimulated.

The technique of induction was, after preparation of the patient and the administration of an enema, to set up an intravenous infusion of dextrose in water solution (5 per cent), each 500 ml. containing 10 I.U. (1.0 ml.) of oxytocin, and to commence the infusion at a rate of 10 to 20 drops per minute. The infusion was continued throughout labor, and for some time after the delivery.

Sedation in the first stage of labor was standardized (meperidine, scopolamine, and promazine), and the amount given varied only with the length of the labor.

The forceps deliveries were of the simple outlet type except for three midforceps applications.

With the patient in lithotomy position in the delivery room, prepared and draped, the bladder catheterized, and the fetal head on the perineum, a No. 20 gauge, 1½ inch needle attached to a 20 ml. oiled heparinized Luer-Lok syringe was introduced into the intervillous space of the placenta through the anterior abdominal wall and anterior wall of the uterus.

At first we limited the intervillous tap to sites 1 to 2 inches below the umbilicus. Later, however, we found that the area of maximal placental souffle most often yielded positive taps. With steady negative pressure applied to the syringe, the needle was introduced slowly until there was a free flow of blood into the syringe barrel. Approximately 3 to 4 ml. of intervillous space blood was withdrawn under anaerobic conditions. The placenta was implanted posteriorly in approximately 50 per cent of the cases, resulting in negative taps. The posterior position of the placenta was confirmed by manual removal subsequent to delivery.

The umbilical cord blood specimens were obtained as follows: Immediately after delivery, and usually within one minute of the intervillous space tap, before the first inspiratory gasp had been taken, a 6 inch segment of cord was isolated by doubly clamping, the maternal clamp being applied first. This segment of cord was then resected and handled extremely gently. Prepared oiled and heparinized Luer-Lok syringes were used to aspirate separately samples of blood from the umbilical vein and arteries. The blood samples were immediately taken to the laboratory and placed in an automatic rotator to ensure their constant and even admixture. All laboratory estimations were done within 30 minutes of the sampling.

All blood samples were drawn and all laboratory work was carried out by one or other of the investigators. The following cases were eliminated from the study: (1) posterior location of placenta; (2) delay greater than one minute between intervillous space tap and clamping of the cord; (3) cord around the neck; (4) cord arterial samples of less than 1 ml.

Approximately 60 per cent of the cases were discarded for at least one of these reasons. In the laboratory we used the Beckman DU Spectrophotometer with the Waters "N" cuvette as described by Nahas[24, 25] for estimating directly the oxygen saturation of our blood samples. The spectrophotometric method was preferred to the more standard gasometric methods, such as the Van Slyke,[26] because the results obtained with the former are not influenced by inhalation of anesthetic gases administered during labor.

The work of Roddie, Shepherd, and Whelan,[27] in addition to our own preliminary studies, verified the close correlation between the results obtained by the spectrophotometric and gasometric methods.

In estimating the oxygen saturation, three separate readings were made on each blood

Table I. Cases in which oxytocin was administered*

Type of delivery	Anesthesia	Oxygen saturation (%)				Partial pressure of oxygen (mm. Hg)				Apgar score
		IVS	UV	UA	V-A	IVS	UV	UA	ΔpO_2	
Spontaneous		65.6	62.5	28.0	34.5	34.0	26.6	15.0	13.2	–
Spontaneous		37.3	24.3	2.2	22.1	21.5	12.2	0	9.3	10
Spontaneous	Cyclopropane and nitrous oxide	98.2	61.0	12.1	48.9	70.0	24.0	8.2	54.0	7
Outlet forceps	Cyclopropane	92.9	67.8	62.1	5.7	62.0	27.0	24.0	36.5	9
Outlet forceps	Saddle block	80.0	33.1	8.5	24.6	41.5	15.3	7.5	30.1	5
Midforceps	Saddle block	51.0	14.5	3.8	10.7	26.5	8.8	0	17.8	2
Lower segment cesarean section	Spinal	66.9	61.1	34.5	26.6	33.2	23.8	15.8	13.4	9
Lower segment cesarean section	Spinal	62.3	35.9	6.1	29.8	30.8	16.0	5.0	20.2	10
Average		69.3	45.0	19.7	25.4	39.9	19.2	9.4	24.3	7.4

*UV = umbilical vein; UA = umbilical artery; IVS = intervillous space; V-A = difference between oxygen saturation in UV and UA.

Table II. Cases in which oxytocin was not administered*

Type of delivery	Anesthesia	Oxygen saturation (%)				Partial pressure of oxygen (mm. Hg)				Apgar score
		IVS	UV	UA	V-A	IVS	UV	UA	ΔpO_2	
Outlet forceps	Nitrous oxide	67.6	55.1	35.0	20.1	35.8	23.2	17.4	15.5	–
Outlet forceps	Cyclopropane and nitrous oxide	80.7	45.2	2.6	42.6	44.7	21.9	0	22.8	7
Outlet forceps	Cyclopropane and nitrous oxide	88.4	78.4	45.4	33.0	54.0	34.2	19.2	27.3	1
Outlet forceps	Cyclopropane and nitrous oxide	38.8	36.0	21.3	14.7	22.4	16.3	11.3	8.6	10
Outlet forceps	Pudendal and nitrous oxide	66.3	56.9	10.5	46.4	32.8	23.0	7.8	17.4	7
Outlet forceps	Pudendal	44.5	51.7	29.2	22.5	24.0	21.0	14.2	6.4	9
Outlet forceps	Pudendal	74.7	54.4	18.1	36.3	37.8	21.8	10.6	21.5	10
Outlet forceps	Cyclopropane and nitrous oxide	91.9	63.7	25.8	37.9	62.5	25.3	13.0	43.4	9
Midforceps	Pudendal and nitrous oxide	52.9	28.8	5.2	23.6	27.0	13.0	5.0	18.0	8
Midforceps	Saddle block	87.7	58.9	19.9	39.0	53.9	25.0	12.1	35.4	8
Lower segment cesarean section	Spinal	82.3	45.1	12.6	32.5	46.6	20.0	9.5	31.8	8
Average		70.5	52.2	20.5	31.7	40.1	22.2	10.9	22.6	7.7

*UV = umbilical vein; UA = umbilical artery; IVS = intervillons space; V-A = difference between oxygen saturation in UV and UA.

sample. Partial pressures of oxygen were then obtained by applying the saturation levels against a standardized dissociation curve.[28]

The oxygen pressure gradient ΔpO_2 was then calculated according to a formula:

$$\Delta pO_2 = pO_2 \text{ maternal} - \left(\frac{[pO_2 \text{ UV} + pO_2 \text{ UA}]}{2}\right)$$

Where UV = umbilical vein and
UA = umbilical artery.

Results

The results obtained are shown in Table I (oxytocin cases) and Table II (non-oxytocin cases).

It will be seen that the figures in the two series were essentially of the same order. In Table I the average oxygen saturation of the blood in the intervillous space, umbilical vein and umbilical artery were 69.3, 45.0, and 19.7 per cent, respectively. In Table II the corresponding figures were 70.5, 52.2, and 20.5 per cent.

In Table I the average partial pressures of oxygen in the intervillous space, umbilical vein, and umbilical arteries were 39.9 mm. Hg, 19.2 mm. Hg, and 9.4 mm. Hg. The corresponding figures in the non-oxytocin cases (Table II) were 40.1 mm. Hg, 22.2 mm. Hg, and 10.9 mm. Hg.

The average oxygen pressure gradient (ΔpO_2) in the oxytocin cases (Table I) was 24.3 mm. Hg compared with 22.6 mm. Hg in the non-oxytocin cases. There was not any apparent correlation between the results obtained, and the method of delivery employed.

Comment

It is by now fairly well established that oxygen crosses the placental barrier from the maternal to the fetal circulation due to a difference in partial pressure of the gas on each side of the membrane, the maternal being the higher. This difference in oxygen tension determines the rate of oxygen supply to the fetus and is defined as the oxygen pressure gradient.

It appears that alterations in the rate of supply of oxygen to the fetus depend to a large extent on the intervillous space saturation. This was first demonstrated by the work of Prystowsky,[1] who showed a diminution in the oxygen saturation of the intervillous space in cases of eclampsia as compared with normal pregnancies, yet the oxygen saturation in the umbilical vessels was similar in the normal and abnormal pregnancies.

The results in this study seem to indicate that there was not any significant difference in this respect whether the labor was spontaneous in onset or whether it was induced or stimulated with oxytocin.

In two of our cases, it was noted that a free flow of blood was obtained from the intervillous space at the height of a uterine contraction. As shown in the previous studies,[2, 20-23] there is increased filling of the intervillous space and rise in manometric pressure during a uterine contraction.

Utilizing the Apgar index[29] for evaluating the clinical condition of the newborn, we found no constant relationship between the pressure gradient and the Apgar score; the scores were the same in our two series.

Summary

Eight cases of oxytocin-induced and stimulated labor have been compared with 11 cases of spontaneous labor with regard to rate of fetal oxygenation (oxygen pressure gradient) and clinical state of the newborn. No difference has been demonstrable in the two series in either respect. No correlation was found between the oxygen pressure gradient and the clinical condition of the infant at birth.

We have found no evidence that oxygenation of the fetus in utero, as measured by the maternal-fetal oxygen pressure gradient is adversely affected by the administration of oxytocin.

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Beta hemolytic streptococcus Group B associated with problems of the perinatal period

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A LIMITED epidemic of throat infections caused by beta hemolytic streptococci occurred in New Orleans from January through March, 1958. Grouping and typing of the streptococci which were made available through the facilities of the Laboratory Section of the Louisiana State Board of Health, and the Communicable Disease Center of the United States Public Health Service at Chamblee, Georgia, showed that the organisms belonged to Group A, Type 12. This unrelated episode led to the present study of the occurrence and significance of beta hemolytic streptococcus Group B. During this period 3 infants who had streptococcal meningitis were admitted to Charity Hospital. The organisms which were isolated from the spinal fluid of these newborn children were typed, along with the streptococci isolated from the throats of the other patients, and proved to be beta hemolytic streptococcus Group B. Two of the 3 infants died.

During this 3 months' period, a total of 36 cultures of beta hemolytic streptococci were typed, 27 were found to belong to Group A and 9 to Group B. As seven of the 9 beta hemolytic streptococcus Group B organisms that were isolated appeared to be the etiological agent of infectious processes, it seemed timely to initiate a study to determine the extent of this problem at Charity Hospital. The initial epidemic had subsided so streptococcus typing was no longer available, except for special cases, but the Louisiana State Board of Health Laboratory agreed to determine the streptococcus groups for this investigation.

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Background

Innumerable studies on the streptococci attest to the importance that has long been attributed to this group of organisms. Holman[26] recognized that the hemolytic streptococci are more virulent than those of the viridans group and offered a classification based on hemolysis and carbohydrate reactions. United States scientists early became interested in the biology of the streptococci[13] and in the relationship of streptococci isolated from cows with mastitis and those which produced infections in humans.[1, 2, 8, 28, 37] Ayers and Rupp[3] showed that cultures of the bovine organisms, in contrast to those from human sources, produced less hemolysis on blood agar and higher acidity in dextrose broth and hydrolyzed sodium hippurate. They concluded that this organism which was named *Streptococcus mastitidis* was not pathogenic for man when consumed in milk. The

same conclusion was drawn from work done at the University of Wisconsin.[21] Ruth,[36] however, isolated a faintly hemolytic streptococcus from the tonsils and placenta of a woman who had had repeated abortions. When this organism was injected intravenously into rabbits, it produced spontaneous abortion in 4 pregnant rabbits and hemorrhage in the uterus of 8 out of 10 rabbits that were not pregnant. The British workers[19, 33] recognized that they were dealing with 2 types of streptococci which they designated as hemolytic and nonhemolytic. They[6] differentiated between *Streptococcus pyogenes* (hemolytic) which they associated with severe puerperal infections and believed of exogenous origin and the nonhemolytic endogenous streptococci that were frequently encountered. They concluded that the nonhemolytic streptococci were normal body saprophytes but were opportunists in that certain untoward factors allowed them to become pathogens. Williams,[46] too, stated that the nonhemolytic streptococci are frequently present in the genital tract of pregnant women and act as pathogens only after some traumatizing of the tissues. The same principle is evident in streptococcal infections of animals.[42] Trauma and/or exposure to cold may initiate the difficulty although *Streptococcus agalactiae* is the immediate cause of disease.

The work of Lancefield[29, 30] laid a foundation for understanding and further scientific investigation of this confusing group of organisms. She discovered that streptococci contain a carbohydrate substance C that determines the group specificity. By a precipitin test, she was able to divide the organism into groups and noted that the various groups were associated with specific origins: A, man; B, cattle; C, various animals; D, cheese; E, certified milk; unclassified, man and cattle. Lancefield and Hare,[31] relating these findings to problems of pregnancy, found that frank puerperal sepsis was caused by beta hemolytic streptococcus Group A in the patients which they studied. Streptococcus Group B organisms were frequently isolated postpartum from the genital tract of women who had an afebrile puerperium or showed evidence of minor infection at this time. Hare and Colebrook[23] isolated beta hemolytic streptococci from the genital tract of 10.1 per cent of the women whom they studied but only 0.95 per cent were *Str. pyogenes* (Group A). Most of the strains appeared similar to those isolated from cases of bovine mastitis. Fry[22] of London reported finding beta hemolytic streptococcus Group B infections in 7 of 211 patients who had streptococcus infections during the puerperium. Three of these 7 patients died. Similar results were obtained by Hill and Butler[24] of Australia who found that Group B accounted for 12 of the 110 streptococcal puerperal infections in their hospital. Seven of these infections were mild, 1 moderate, and 4 severe. All 4 patients with severe infections died.

Further investigation was made by Lancefield and Hare[31] in an effort to explain the presence of streptococci in relation to infections in the parturient. Streptococci Group B were not isolated from any of the 46 women studied who had severe puerperal sepsis. Seven of the 16 vaginal cultures made from women who had minor postpartal infections showed organisms that belonged to Group B. Lancefield[32] stated that only beta hemolytic streptococcus Group A was likely to be a human pathogen but listed 38 fatal human infections reported in the literature which were caused by streptococci of the other groups. Beta hemolytic streptococcus Group B accounted for 20 of these infections, 14 of which had produced puerperal sepsis.

In spite of these reports, there is still a tendency to discount the clinical importance of beta hemolytic streptococcus Group B.[17, 40, 44]

The current work in this field comes from Holland. De Moor[11] stated that beta hemolytic streptococcus Group B is cultured regularly from the throat, rectum, and vagina of approximately one out of every 3 of his patients. He considers its pathogenicity almost nil except for an occasional case of endocarditis or septicemia or acute, usually fatal, meningitis in newborn infants.

Bacteriology

The members of beta hemolytic streptococcus Group B have several identifying characteristics.

1. The carbohydrate specific for the group can be demonstrated by the Lancefield precipitin test.

2. The zone of hemolysis which usually surrounds the colonies is much narrower and less definite than that produced by Groups A, C, or G. Some Group B organisms are nonhemolytic.

3. The hemolysis is usually not inhibited by bacitracin differentiation discs.

4. The colony has a softer consistency than that of Group A and can be picked up more easily on a needle.

5. The final pH produced by growth in 1 per cent glucose broth falls between 4.2 and 4.8, more acid than the 5.2 to 5.8 produced by similar growth of the Group A organisms.

6. This organism will grow on 40 per cent bile agar which almost completely inhibits the growth of Group A streptococci.

7. Sodium hippurate is hydrolyzed.

8. The organism will not dissolve human fibrin.

9. Carbohydrate reactions and physical conditions influencing growth are irregular or similar to those produced by Group A.

The accepted name for the type organism, according to *Bergey's Manual of Determinative Bacteriology*,[7] is *Str. agalactiae*. *Str. mastitidis* is considered a synonym. The source of *Str. agalactiae* (Group B) is given as the milk or udders of cows or the human urogenital tract.

The validity of the identification of our organisms as beta hemolytic streptococcus Group B was based on part of the mentioned tests.

1. Precipitin tests were done by the Laboratory Division of the Louisiana State Board of Health.

2. The weak hemolysis was the characteristic that initially called attention to the organism.

3. "Strep A" (bacitracin) discs failed to inhibit the growth of these organisms.

4. The colony texture was characteristic of that described for the streptococci of Group B.

5. Sixteen of the beta hemolytic streptococcus Group B were grown in glucose broth for 48 hours and the pH tested. All of the organisms designated as Group B by other tests produced a final pH between 4.2 and 4.8 in contrast to the pH of 5.2 to 5.6 produced by the Group A controls.

Many sensitivity studies with the disc method showed these organisms to be almost uniformly sensitive to penicillin, erythromycin, tetracycline, and chloramphenicol.

Epidemiology

The early work of Lancefield[29] showed that the most characteristic source of beta hemolytic streptococcus Group B was from cattle that had mastitis. The English authors Minett, Stableforth, and Edwards[34] divided the bovine streptococci into 3 divisions, I, II, and III, in which Group I produced chronic mastitis, Group II mastitis of an acute form, and Group III a very mild disease process. Precipitin tests showed that only Group I belonged in the Lancefield streptococcus Group B. Stewart[43] also found that the *Str. agalactiae* isolated from cases of bovine mastitis belonged to the English Group I or Lancefield B. Lancefield[32] further divided streptococcus Group B into serologic Types Ia, Ib, II, and III. She tested 68 organisms from human sources, some of which appeared unrelated to, some were associated with, and still others seemed to be the cause of disease. She found representatives in each type but a preponderance were derived from nonpathogenic sources. Organisms isolated from bovine mastitis were also included in each type. The Dutch workers[12] found that 95 per cent of their human strains but only 70 per cent of the bovine strains of beta hemolytic streptococcus Group B could be placed in the Lancefield types. Dr. Lancefield typed 16 of the beta hemolytic streptococcus Group B isolated at Charity Hospital. A statement concerning the clinical problem of each source patient is given together with the type.

Ia. 5 mothers who had abortions or were delivered of stillborn infants

1 dead fetus

1 mother who had a premature child

1 infant who died from meningitis

1 case of osteomyelitis

Ib. None

II. 3 control cultures on well infants

1 throat culture of infant not seriously ill

1 culture from the eye of infant not seriously ill

1 urine culture from pregnant woman

III. 1 mother who had an incomplete abortion

If any deductions could be allowed from this small number, it would seem that Type Ia of the beta hemolytic streptococcus Group B is the most prevalent in this area and comprises the most serious infections. The English workers[19] showed that the streptococci isolated from the vaginas of afebrile pregnant women or those who had mild puerperal infections were culturally and biochemically indistinguishable from the organisms that produce mastitis in cows. Simmons and Keogh[38] believed beta hemolytic streptococcus Group B to be of great economic importance among cattle in Australia but of little significance in people. They found no cross-agglutination between bovine and human beta hemolytic streptococcus Group B so they believed that cross-infection could not occur. De Moor[12] studied 4 different organisms that are included in Group B and found that only *Str. mastitidis* was isolated from both human and bovine sources and *Str. agalactiae* from bovine only. Even so, he believed that the organisms isolated from human and bovine sources represented separate entities. Bergey[7] gives *Str. mastitidis* as a synonym of *Str. agalactiae* and it is so considered in the United States.

A detailed study of the hemolytic streptococci in Puerto Rico[35] showed that beta hemolytic streptococcus Group B was rarely found in human cultures (2 per 657). They stated, however, that this was a biased observation as their studies in humans were directed toward the streptococci that produced the most pronounced zone of hemolysis. Bovine mastitis was common, and the Group B streptococcus was isolated from 90 per cent of the 130 cows cultured.

Cole[9] states that this subject warrants pursuing not only to learn the extent of its occurrence and possible pathogenicity but to determine the relation between the organisms isolated from human and animal sources.

It seems evident from the many investigations pursued over the years, some of which are reported above, that the status of beta hemolytic streptococcus Group B is still not clearly established. Three questions, one clinical and 2 epidemiologic, remain without satisfactory answers.

1. Does beta hemolytic streptococcus Group B produce serious human infections?

2. Is the organism isolated from people the same as the one that causes bovine mastitis?

3. If the organisms are the same, is the human infection contracted from cows?

Each question calls for further investigation but only the first lends itself to study in a hospital environment. The work quoted has established that beta hemolytic streptococcus Group B is associated with problems of pregnancy. The large obstetric service at Charity Hospital seemed to provide an ideal setting in which to seek an answer to the clinical question posed, "Does beta hemolytic streptococcus Group B produce serious human infections?"

Present study

Beta hemolytic streptococcus Group A has rightly claimed the major attention as the etiological agent of human disease throughout the years. The precipitin test of Lancefield applied to many streptococci isolated during the period following her work showed that 90 to 95 per cent of the streptococci isolated from human infections belonged to Group A. This estimate is still frequently quoted[41] even though the clinical manifestations of streptococcal infections have been greatly changed over the years.[16] Present workers have tended to discount the impor-

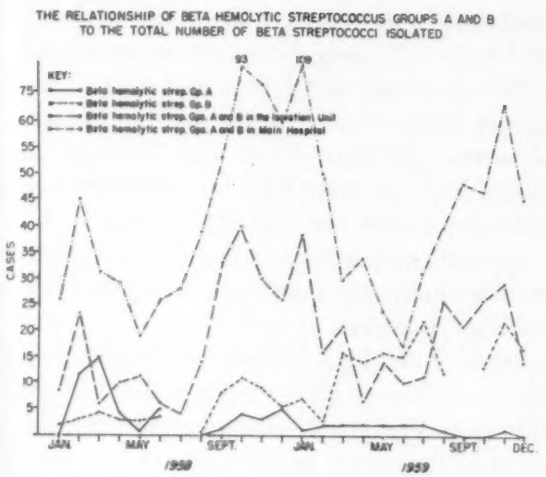

Fig. 1. The relationship of beta hemolytic streptococcus Groups A and B to the total number of beta streptococci isolated.

tance of streptococci other than Group A in human infection.[38]

The current picture at Charity Hospital, with the exception of scattered episodes, seems to show that beta hemolytic streptococcus Group B is being isolated in increasing numbers from patients with infections while Group A frequently appears as an incidental finding primarily in throat cultures. A study was made to test the validity of this observation.

A comparison was made for a test period of January to June, 1958, between the number of beta hemolytic streptococcus Group A organisms isolated with the number of alpha hemolytic streptococci found primarily in throat cultures and considered as normal flora. The incidence of the latter remains fairly constant throughout the year. Beta hemolytic streptococcus Group A was found to comprise from 2 to 3 per cent of the streptococci isolated from patients in the Main Hospital Building with an increase to 5.6 per cent during the streptococcus epidemic of January to March, 1958. The beta hemolytic streptococcus Group A prevalence in the Isolation Division of Charity Hospital was about 6 per cent of the streptococci isolated and showed an elevation to 15.5 per cent during the 1958 epidemic. The basic prevalence for the groups was roughly reestablished by July, 1958.

Other observers have discounted the significance of finding an occasional beta hemolytic streptococcus Group A in the throat. Zanen and associates[47] concluded, after a 2½ year continuous study of throat cultures in Amsterdam, that the finding of this organism had very little diagnostic importance. Cornfeld and associates[10] observed that about half of the children studied in Philadelphia carried beta hemolytic streptococcus Group A in their throats some time during the year regardless of prophylactic therapy and noted that the clinical manifestations were minimal.

The low incidence of acute infections caused by beta hemolytic streptococcus Group A focused our attention on the apparently increased prevalence of the beta hemolytic streptococcus Group B which were isolated primarily from the female genital tract and appeared to be involved in problems of the perinatal period. The years 1958 to 1959 were chosen as the study period. The streptococci that seemed most clearly identified as the etiological agent in infections were typed. Groups A and B so predominated that only they are included.

Fig. 1 shows the beta hemolytic streptococcus Groups A and B found at Charity Hospital for the years 1958 to 1959. These organisms isolated primarily from infections are shown in relation to the total numbers of beta hemolytic streptococci isolated. Data are presented separately for the isolation unit and the main hospital.

These data are admittedly biased as it was impractical to have all of the streptococci typed. The predominance of Group B over Group A, however, is obviously marked except during January to March, 1958, the period of the epidemic of sore throats referred to previously. Sixty-five of the 275 beta hemolytic streptococci, which were typed, fell into Group A and 210 into Group B. Group A organisms were isolated primarily from abscesses and infections of the respiratory tract (55 out of 65) while those of Group B were largely associated with difficulties experienced during the perinatal period (171 out of 210) (Table I).

Table I. Prevalence of beta hemolytic streptococcus Groups A and B in relation to types of infections

Types of infections	*Group A*	*Group B*
Abscesses and respiratory infections	55/65 (84.6%)	33/210 (15.7%)
Perinatal problems, mother and/or child	7/65 (10.7%)	171/210 (81.4%)

It is obvious from these data that the beta hemolytic streptococcus Group B was associated with problems of the perinatal period. The types of abnormalities encountered are given in Table II.

The organism is obviously not only present in the genital tract of pregnant women but is frequently associated with the most serious complications of this period. Beta hemolytic streptococcus Group B in the urinary tract may produce local infection but no accompanying complications of pregnancy were noted if the organism was limited to this area.

Two explanations of the above observations are possible: (1) beta hemolytic streptococcus Group B is an organism that causes human infections, primarily of the perinatal period, or (2) beta hemolytic streptococcus Group B is part of the normal flora of the female tract. It may be isolated and appear to be the etiological agent when cultures are made from women who are experiencing difficulty during the perinatal period.

Several studies have been carried out in an attempt to determine which of these possibilities is correct.

Table II. Clinical problems in 171 patients or infants where beta hemolytic streptococcus was isolated

Organisms isolated from genital tract of mother or brain or blood of child		
Serious complications		56
Abortion (under 600 grams)	11	
Perinatal death	26	
Premature birth but lived	15	
Serious illness of child with recovery	4	
No serious complications		95
Organisms isolated from urinary tract of mother but also found in genital tract		
Complications		2
Abortion	1	
Premature birth	1	
Organisms isolated from urinary tract only		
No complications		20

Study I. If beta hemolytic streptococcus Group B is part of the normal flora of the human genital tract and therefore only incidentally present in cultures made when untoward conditions develop during the perinatal period, it should be possible to culture these organisms from a relatively constant percentage of unselected pregnant women.

Procedure. Two to 5 Gm. of placenta was taken for culture from 208 unselected women at the time of a presumably normal delivery. This material was immediately placed in 8 ml. of brain-heart infusion agar. The organisms were isolated and identified in the Department of Bacteriology. Beta hemolytic streptococcus Group A was not encountered but beta hemolytic streptococcus Group B was isolated from 11 out of 208 or 5.2 per cent of the specimens cultured. Alpha hemolytic streptococcus, usually accepted as normal flora of the female genital tract, was isolated in 41 out 208 instances or 19.7 per cent. Few complications were noted in either group, but 3 of the women from whom beta hemolytic streptococcus Group B was isolated were delivered of premature infants (3 out of 11) while in contrast 4 premature births were noted in the group harboring alpha hemolytic streptococci (4 out of 41).

Study II. It was proposed to obtain cervical cultures from approximately 100 pregnant women at the time of their first visit to the obstetric clinic and again at the time of delivery. It was hoped that this would indicate whether or not the presence of beta hemolytic streptococcus B contributed to the hazards of pregnancy. Not enough second cultures were obtained to make such observations possible so only the first group of cultures are reported.

Procedure. Cervical cultures were obtained from 118 pregnant women at their first visit to the obstetric clinic. Six or 5.8 per cent yielded beta hemolytic streptococcus Group B. Alpha hemolytic streptococcus was isolated 34 times, or from 28.8 per cent of the individuals.

The above data indicate that between 5 per cent and 6 per cent of pregnant women of this area harbor beta hemolytic streptococci Group B in the genital tract with no apparent ill effects.

Study III. Hoeprich[25] reported that *Listeria monocytogenes* may be found in abundance in the meconium of infants that have acquired listeriosis in utero. Accepting this premise, it could be deduced that beta hemolytic streptococcus Group B would be present in the meconium of premature infants in a higher proportion than found in cultures from unselected pregnant women if this organism had contributed to the prematurity.

Procedure. Meconium cultures were taken on 79 premature infants as soon as they reached the Premature Center. Four of these cultures yielded beta hemolytic streptococci Group B (5.09 per cent) which is approximately the number which might be expected to occur from maternal contamination, judging from the apparently basic flora of pregnant women of this area.

Study IV. A special study to determine the role of *L. monocytogenes* related to serious problems of pregnancy was being carried on concomitantly.

Procedure. Cultures of the vagina, cervix, and uterus were submitted from the mother and appropriate cultures from any apparently infected area of the child; cord blood, eye, ear, or brain, if a dead fetus was delivered. Listeria was isolated from one mother and her dead fetus. Beta hemolytic streptococcus A was not encountered in this series but beta hemolytic streptococcus Group B was isolated from 16 of the 66 mothers from whom cultures were taken (24.5 per cent). Four organisms morphologically and culturally typical of this organism are not included, as one was reported nonviable at the typing center and 3 others were not typed. These added to the above number give presumptive evidence that 20 out of 66 (30.3 per cent) of the mothers in this series who exhibited marked difficulties during the perinatal period harbored beta hemolytic streptococcus Group B in the genital tract. Twenty-one of the infants born of these mothers were cultured and beta hemolytic streptococcus Group B was isolated from 8. Of these 8 infants, 5 experienced neonatal death and 2 others were born prematurely but developed normally in the Premature Unit.

Study V. If beta hemolytic streptococcus Group B contributes to the tragedies of pregnancy, one should be able to recover this organism from the brains of dead fetuses and stillborn infants in greater numbers than the approximately 5 per cent that appears to be part of the normal flora of the genital tract of pregnant women in this area.

Procedure. One hundred and thirteen cultures were made, 66 from brains of fetuses that weighed less than 500 grams and 47 that were over that weight, including fully developed stillborn infants. Beta hemolytic streptococcus Group B was isolated 11 times, giving a 9.7 per cent incidence. Divided according to infant weights, this organism was found in 7 of the small fetuses (10.6 per cent) and in 4 of the larger (8.5 per cent). The numbers are too small for statistical evaluation but it appears that beta hemolytic streptococcus Group B may be involved in early loss of the fetus.

Study VI. An approach to the answer of the question as to whether beta hemolytic streptococcus Group B plays the role of a pathogen or a bystander in problems of pregnancy was suggested by the work of Benirschke and Clifford.[5] They made histologic examinations of frozen sections of umbilical cords and interpreted vasculitis as the result of neonatal infection.

Procedure. Approximately 3 cm. of the umbilical cords of 100 unselected infants were placed in 10 per cent formalin for conventional sectioning. Cultures were made in brain-heart infusion agar of 2 or 3 Gm. of an adjoining piece of each of the cords. The sections were examined by a pathologist and

Table III. Summary of special studies to determine the significance of cocci isolated in the perinatal period

	Study I, 208 apparently normal placentas		*Study II, cervical cultures 118 first clinic visits*		*Study III, meconium in 79 cases*		*Study IV, 66 serious problems of pregnancy*		*Study V, brains of 113 dead fetuses or stillborn infants*		*Study VI, 100 cord cultures*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Beta hemolytic streptococcus A	0	0	0	0	0	0	0	0	0	0	0	0
Beta hemolytic streptococcus B	11	5.2	6	5.8	4	5.0	16	24.2	11	9.7	6	6
Alpha hemolytic streptococcus	43	20.6	34	28.2	2	2.5	7	10.6	18	15.8	30	30
Enterococcus	22	10.5	0	0	1	1.2	8	12.1	4	3.5	7	7
Staphylococcus epidermidis	92	44.2	60	50.8	12	15.1	16	24.2	26	23.0	30	30
Staphylococcus aureus	1	0.48	3	2.5	3	3.8	7	10.6	5	4.4	1	1

the organisms were isolated and identified independently in the bacteriology laboratory. Seventeen of the cords showed more or less infiltration of the vein wall, while beta hemolytic streptococcus Group B was isolated from only 6 of the cultures. Examination, however, showed no overlapping; none of the cords from which these organisms were cultured exhibited any degree of infiltration. This then did not give the answer but it agreed with the basic observation that beta hemolytic streptococcus Group B appears to be part of the normal flora of the genital tract of from 5 to 6 per cent of pregnant women. It may then become part of the naturally acquired flora of the young without producing disease. These results are consistent with those found by Dominguez and associates[14] who studied leukocytic infiltration of the umbilical cord. They concluded that this phenomenon was caused by interference with the normal flow of blood in the umbilical vessels and indicated fetal distress due to hypoxia rather than fetal infection.

Beta hemolytic streptococcus Group B and *Staphylococcus aureus* were the only cocci that showed an increased prevalence in patients who experienced major difficulties during the perinatal period (Studies IV and V). These data do not lend themselves to statistical evaluation. If, however, beta streptococcus Group B were isolated only because cultures were made at the time of special stress during the perinatal period, the percentage of isolations should be the 5 to 6 per cent shown in Studies I, II, III, and VI. The increase to 24.2 per cent seems conclusive that this organism is involved as one cause of at least some of the difficulties of the perinatal period.

Comment

Maternal and infant morbidity and mortality have long been the concern of civilized countries.[45] Concerted action in one area[4] which was able to reduce the maternal mortality 70 per cent only lowered the infant mortality by 16 per cent. Since more than half of the infant deaths occurred in babies born before term it seemed evident that prematurity was a major cause of this loss. The Children's Bureau of the United States Department of Health, Education, and Welfare reported that the postnatal death rate of infants born in the United States between 1942 and 1955 was cut in half while the perinatal rate was reduced less than one third. Three out of 5 of these neonatal deaths occurred in infants born prematurely. Some abnormality causes the mother to give birth before term which greatly increases the risk of death.[18]

Infection has not been considered a prime cause of neonatal death.[18] Different groups

have estimated its importance in this problem to be from 3.3 to 14.3 per cent. Prematurity in these same groups, however, was 40 and 41 per cent, respectively.[15, 20]

According to Smith,[39] the infant mortality rate which declined in the United States from 1952 to 1956 has since risen. Infection is not the most important cause of this increase in neonatal mortality but is one for which control measures are known. Smith believes that bacterial infection in premature infants is the result of maternal infection which probably begins by producing amnionitis in the mother, crosses the membranes, infects the fetus, and frequently results in a premature birth. *Staph. aureus* and *Escherichia coli* were the organisms that caused most concern for the Boston group.[39]

The present work calls attention to an infection that has been largely discounted in the United States. Two hundred and ten of the 275 strains of beta hemolytic streptococci which were typed proved to belong in Group B and 81.4 per cent of those (171 out of 210) were associated with problems of the perinatal period. The clinical manifestation in the mother was fever that usually resulted from amnionitis and/or endometritis which for the most part disappeared after delivery. The complications in the infant were more serious. Abortion, perinatal death, premature birth or serious illness with final recovery were noted in 56 of the infants born of the 151 mothers who were shown to have beta hemolytic streptococcus Group B in the genital tract (37.0 per cent).

Thirty-three (15.7 per cent) of the persons from whom this organism was isolated were not pregnant but a number of them had debilitating diseases such as diabetes, leukemia, or tuberculosis. This pattern is noted in *L. monocytogenes* infections[27] in that pregnant women are often involved but recover following delivery. The greatest damage is suffered by the infant who may have acquired the infection in utero or during the birth process. The comparison can be carried farther in that *Listeria* infections in persons other than those who are pregnant are usually found in already debilitated adults.

The causes of perinatal death are multiple and prematurity increases the danger manyfold. These data show that beta hemolytic streptococcus Group B, which has been largely discounted as a human pathogen, is certainly associated with and apparently the cause of some of the perinatal difficulties including prematurity. Recognition of this infection accompanied by appropriate action will give an additional approach toward control of this very serious problem.

Conclusions

1. Beta hemolytic streptococcus Group B has been frequently isolated from the patients of Charity Hospital.
2. Two hundred and ten of the 275 strains of streptococci that were typed in this study belonged to Group B.
3. Of the 210 patients involved, 171 were pregnant women.
4. The organism was isolated from the genital tract of 151 and from the urinary tract of the additional 20 patients.
5. The clinical manifestation in the mothers for the most part disappeared following delivery.
6. Complications of abortion, perinatal death, prematurity, or severe illness with ultimate recovery was noted in 56 out of 151 or 37.0 per cent of the infants born of these mothers.
7. Control studies showed that beta hemolytic streptococcus Group B was present in the genital tract of from 5 to 6 per cent of the pregnant women admitted to this hospital without evidence of producing disease.
8. As this organism was isolated from 16 out of 66 or 24.2 per cent of a group of patients who experienced marked difficulty during pregnancy and from 11 out of 113 or 9.7 per cent of brains of dead fetuses and stillborn infants, it is concluded that beta hemolytic streptococcus Group B may well be the etiological agent in some of these problems of the perinatal period.

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Staphylococcal infection among mothers and infants

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STAPHYLOCOCCAL infections have been increasing in importance in recent years. Particularly, the resistant staphylococcus has become a major hospital problem.

Not only in American and in European countries, but also in Japan, the origin of cross infections has become a big problem. In the obstetrical field, skin infections of the newborn or postpartum mastitis occurring during the period of hospitalization has increased, and an effective campaign is now very desirable.

We are reporting here our study on the staphylococcus at the Juntendo Hospital, with special regard to the pathogenic staphylococcus, its resistance to antibiotics, the characteristics of the phage types, the present conditions for the spread of resistant strains in the hospital, and the course of cross infections.

Materials and methods

The experience is based upon the following: (1) 1,050 strains of staphylococcus isolated from various parts of the body (nasal cavity, nipples, milk, fingers, and vagina) of postpartum patients who were admitted to this hospital in the 3 year period from Jan. 1, 1956, to the end of 1958; (2) 374 strains which were isolated from the fingers and nose of hospital nurses and physicians and from contact materials such as the floor and the air in the patient's room, sleeping materials, beds, etc. Thus, a total of 1,860 strains of staphylococcus were available for this study.

Aseptic cotton swabs were used to gather the materials, and staphylococcus medium No. 110 (Difco) and Drigalski's medium were used for cultures. Coagulase test, with human plasm, the pigment-producing test (10 per cent milk agar), and the glucose analysis test (mannit) were carried out. At the same time, tests for antibiotic resistance were performed for penicillin, streptomycin, chloramphenicol, tetracycline, and erythromycin on agar plates by dilution methods.

We have characterized the resistance of the strain as the maximum concentration of the drug solution which barely allows its growth. The figure for penicillin is 1 μ per cubic centimeter; for streptomycin, 10 γ per cubic centimeter; for chloramphenicol, 10 γ per cubic centimeter; for tetracycline, 3 γ per cubic centimeter; and for erythromycin, 3 γ per cubic centimeter.

For phage typing we used 20 phage types which were originally sent from Williams Staphylococcus Reference Laboratory, Colindale, London, to the National Institute of Health of Japan, and we obtained them through the latter by their courtesy.

Results of studies

A. Neonatal skin disease and postpartum mastitis. In 3 years, starting at the beginning of 1956, there were 60 cases of neonatal

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Table I. Cases of neonatal skin disease and postpartum mastitis

Disease	1956					1957		
	March-April	*May-June*	*July-Aug.*	*Sept.-Oct.*	*Nov.-Dec.*	*Jan.-Feb.*	*March-April*	*May-June*
Onset during hospitalization								
Impetigo		5 (1)*	10 (1)	4			1	2
Neonatal breast abscesses							1	
Impetigo and conjuctivitis		1						
Neonatal breast abscesses and conjunctivitis								
Conjunctivitis		1				3	2	
Onset after discharge								
Impetigo					1		1	
Postpartum mastitis	4	1	5	1	1	1	1	1

*Figures in parentheses indicate the number of the mothers (among mothers of the diseased babies) who developed postpartum

1957
July-Aug.
7 (1)
2

mastitis

purulent skin disease including impetigo, conjunctivitis, neonatal breast abscess, and some others. The frequency of each and the month of occurrence are shown in Table I.

Among these, impetigo was the most frequent disease, comprising 80 per cent (48 cases) of all. The majority of these lesions appeared from 4 to 6 days after the child's birth (71.7 per cent) (Fig. 1).

Twenty-seven cases of postpartum mastitis developed in the mothers whose baby had impetigo and 18 of these developed breast abscesses. They started within one week of delivery in 14.8 per cent, and 4.8 per cent in 2 weeks and the remainder after 3 weeks. So, the majority occurred after the patient went home (average, 25.5 days).

1. Drug resistance among strains from skin lesions of newborn infants and from puerperal mastitis. From every case of skin disease of the newborn, the staphylococcus was isolated. Among the cases of neonatal impetigo, including the case of abscess in the chest, 88.3 per cent of strains (53 of 60) produced pigment. They were also coagulase-positive and mannit analytic strains.

All strains of staphylococcus isolated from postpartum breast abscesses showed a pigment-producing reaction. They were also coagulase-positive and mannit analytic strains.

As shown in Fig. 2, the resistance for drugs was high and in the order of penicillin, streptomycin, and tetracycline. Strains isolated from cases of impetigo and mastitis manifested about the same tendencies.

In contrast, however, between the years of 1956 and 1958, the resistance to penicillin dropped from 90.5 to 66.7 per cent and that to streptomycin from 61.8 to 44.4 per cent. In this period the resistance to tetracycline increased from 4.8 to 38.9 per cent. These trends are to be explained by the increase of the usage of those drugs.

2. Phage typing in strains from skin lesions of newborn infants and from puerperal mastitis. There was a high percentage of typable strains, namely, in cases of impetigo, 56.1 per cent; in cases of conjunctivitis, 66.7 per cent; and in cases of postpartum mastitis, 88.9 per cent (Table II).

The majority belonged to Group I. With respect to the lytic pattern, 29 was the most frequent among the cases of neonatal impe-

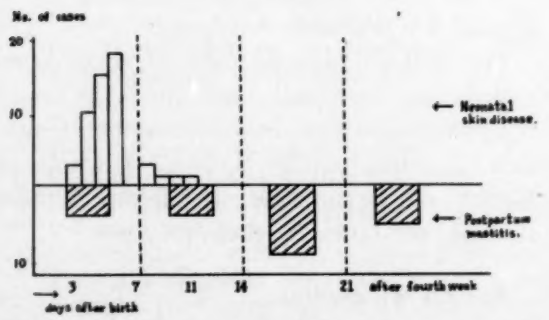

Fig. 1. Frequency of starting day of neonatal skin disease and postpartum mastitis. (Neonatal skin disease occurred most frequently in the first week after birth and postpartum mastitis in the third week.)

1957			1958						1959		
July-Aug.	Sept. Oct.	Nov.-Dec.	Jan.-Feb.	March-April	May-June	July-Aug.	Sept.-Oct.	Nov.-Dec.	Jan.-Feb.	March	Total
7 (1)			1			7 (1)	3	4	3	1	48 (4)
											1
									2		3
							1				1
							1				7
	1						1	1	1		6
2			1		1	3	1		2	2	27

mastitis later.

tigo, this being found in 21 cases. Among the cases of mastitis, pattern 29 was seen in 10 cases, the next most frequent being pattern 52, with 4 cases.

B. Endemiologic factors in hospital infection.

1. Evaluations of mothers and their infants. Cultures of nasal cavities gave the highest frequency of positive results (44.5 per cent) for the pathogenic staphylococcus among normal mothers in the puerperium. This site was followed in order of frequency by the fingers, 34.6 per cent; nipples, 21.9 per cent; and milk, 21.4 per cent. From the vagina, positive cultures were the lowest (only 9.9 per cent).

During the hospitalization of the normal postpartum patients, usually for about a week, the frequency of positive cultures for the pathogenic staphylococcus and for the

Table II. Phage typing on strains isolated from neonatal skin disease and abscess of postpartum mastitis

			Grouping							
			Group I		Group II		Group III		Mixed	
Name of disease	Coagulase-strain	% in typing	Lytic pattern	No. of strain	Lytic pattern	No. of strain	Lytic pattern	No. of strain	Lytic pattern	No. of strain
Newborn infants										
Impetigo	57	56.1 (32)	29	21			77	1	6/7/47/54/29	1
			29/52	1			53	1	29/52/6/7/47/77	1
			29/52A	1					73/79	1
			52	4						
Conjunctivitis	9	66.7 (6)	29/52	1					29/71	1
			29	1						
			52	1						
			29/52/52A/79	2						
Mothers										
Postpartum mastitis	18	88.9 (16)	29	10			7/52/547	1		
			52	4				1		

Table III. Changes in drug resistance of coagulase-positive strains obtained from mothers and infants during puerperium

Part of body	*% of coagulase-positive strain*	*Resistance of coagulase-positive strains (%)*				
		Penicillin	*Streptomycin*	*Tetracycline*	*Chloramphenicol*	*Erythromycin*
Nasal cavity						
Admission	35.3	38.9	11.1	0	0	0
Discharge	43.8	43.8	23.8	4.8	0	0
Nipples						
Admission	21.4	16.7	11.1	0	0	0
Discharge	24.7	30.4	13.0	13.0	0	0
Milk						
Admission	15.4	12.5	12.5	0	0	0
Discharge	22.9	7.1	7.1	7.1	0	0
Fingers						
Admission	31.8	14.3	7.1	0	0	0
Discharge	26.0	23.1	7.7	0	0	0
Vagina						
Admission	4.8	0	0	0	0	0
Discharge	7.1	50.0	50.0	0	0	0
Nasal cavity of infant						
Admission	19.2	0	0	0	0	0
Discharge	65.4	32.1	11.3	3.8	0	0

Table IV. Drug resistance in strains isolated from members of the professional staffs

	Nasal cavity				*Fingers*
	Physicians	*Nurses*	*Special nurses*	*Total*	*Special nurses*
No. of strains	43	41	92	176	53
Penicillin	37.2 (16)	48.8 (20)	54.3 (50)	48.9 (86)	30.2 (16)
Streptomycin	18.6 (8)	24.4 (10)	26.1 (24)	23.9 (42)	9.7 (5)
Chloramphenicol	2.3 (1)	2.4 (1)	2.2 (2)	2.3 (4)	1.9 (1)
Tetracycline	11.6 (5)	22.0 (9)	17.4 (16)	17.0 (30)	9.7 (5)
Erythromycin	0	2.4 (1)	0	0.6 (1)	0

Table V. Phage typing on the strains which are obtained from professional workers

	Nasal cavity						*Fingers*	
	*Physicians (16)**		*Nurses (23)*		*Special nurses (66)*		*Special nurses (21)*	
Phage type	*Lytic pattern*	*No. of strains*	*Lytic pattern*	*No. of strains*	*Lytic pattern*	*No. of strains*	*Lytic pattern*	*No. of strains*
I	29	2	29	4	29, 29/52 29/52A/52/79, 79, 52	14	29 52	2
II			71	1	71	1		
III	6/7/47/54 6/7/47/75	3	6/7/47/54/53	1	53, 75 6/7/47/54/53 others	16	6/7/47/75 70/42E/7/73	2
Mixed					7/29/52A/52/79	1		
Untypable		11		17		34		17
Typable (%)	31.3		26.1		48.5		19.0	

*Number of strains.

antibiotic-resistant strains tended to increase. At the time of the patient's discharge from the hospital, cultures from the nasal cavity had increased to 43.8 per cent as compared with 35.3 per cent upon admission. Resistance to antibiotics also increased in frequency, with the following comparisons: for penicillin, 38.9 per cent upon admission and 47.6 per cent on discharge; for streptomycin, 11.1 per cent on admission and 23.8 per cent on discharge (Table III). The same tendencies were evident in the cultures from nipples and fingers. Among the 75 newborn infants, cultures for staphylococcus became positive from the nasal cavities in 31.9 per cent within 2 days after birth. The positive percentage was increased up to 88.0 per cent at the time of discharge on the seventh to the ninth day after birth.

There was also an evident increase in the frequency of the pathogenic staphylococcus in these cases, namely, from 19.2 per cent 2 days after birth to 65.4 per cent upon discharge from the hospital. The frequency of resistant strains increased to 32.1 per cent for penicillin, 11.3 per cent for streptomycin, and 3.8 per cent for tetracycline, respectively. It is a striking observation that the pathogenic staphylococcus and its resistant strains have reached such a frequency after such a short period after birth in the hospital.

In evaluation of its spread and persistency by means of phage typing, in 8 cases of mothers and their infants who both had coagulase-positive strains upon admission, there were 5 mothers who showed the same phage continuously during the period of hospitalization. There were 3 cases in which the staphylococcus was found to have changed to another strain by the time of the patients' discharge from the hospital.

Among the newborn infants, 7 babies showed the same phage type or an untypable strain until discharge. Another one had a different type of strain upon discharge from the hospital.

With respect to a relationship between the mothers and their infants, there were only 2 cases which showed the same phage staphylococcus, and it was believed that there is no further correlation between them. In spite of the short period of hospitalization, alterations among the resistant strains obtained from nasal cavity or other mucous membranes was a frequent finding.

2. Evaluations in the nursing and medical staffs. Cultures for the pathogenic staphylococcus from the nasal cavity and fingers of the physicians and nurses of the obstetrical department were also carried out. In 37.2 per cent of the physicians (16 of 43), 55 per cent among the nurses (22 of 40), and 72.5 per cent among the attending nurses* (66 of 91), the staphylococcus was found in the nasal cavity.

The resistance to antibiotics of the strains cultured from the professional staffs are shown in Table IV. The strains from the attending nurses were resistant in the highest percentage. In comparison with the yearly decrease of strains resistant to penicillin the increase of the tetracycline-resistant staphylococcus was quite impressive.

With the demonstration of the high percentage of carriers of the resistant staphylococcus among the members of the professional staffs in the hospital, it became important to learn how living conditions would affect the healthy person coming into the hospital for work. The student nurses were studied for this purpose (Fig. 3).

While they were having lessons outside of the hospital, the frequency of carriers of the pathogenic staphylococcus among the student nurses was only 4.1 per cent, but in 3 weeks of hospital work this had increased to 16.6 per cent, and in 12 weeks it became 21.7 per cent. The percentage of the resistant staphylococcus also increased to two times for penicillin and chloramphenicol, three times for streptomycin, and six times for tetracycline. Even in the same hospital, there were some differences between the floors. For example, on the floor for tuber-

*The "attending nurse" in Japan is similar to a special nurse in the United States. She takes care of a mother and her baby on a 24 hour basis during their period of hospitalization but during this time does not take care of other mothers or babies.

culosis, the increase of strains resistant to streptomycin was observed and was considered as quite to be expected.

In 105 strains of staphylococcus which were isolated from the nasal cavities of the professional workers, 31.3 per cent of strains from physicians, 26.1 per cent of those from nurses, and 48.5 per cent of those from attending nurses were phage typable. The figure for strains cultured from the fingers of the attending nurses was 19 per cent.

Among phage types, Groups I and III were the most common, especially the former, which includes the lytic pattern closely related to the causative strains of neonatal impetigo and postpartum mastitis. Among the attending nurses who are always with the newborn infants, some showed long periods of persistent positive cultures, some for as long as 4 months (Table V).

3. Evaluations from materials in obstetrical floor. One hundred and forty-five strains of staphylococcus were isolated from the air in the patient's room (including delivery room), clothes of the newborn infants, sleeping materials, beds, nipples of the milk bottles, and water after a bath. Coagulase-positive strains comprised 28.5 per cent of positive cultures obtained from the air of the patient's room (25 of 87 strains). With regard to phage typing, the majority showed the same lytic pattern as the strains obtained from the professional workers mentioned above.

4. Course of infection. To determine the relationship between the lesions of the neonatal impetigo and persistent staphylococcus, the strains which were isolated from the lesions of impetigo and from the nasal cavity of mothers and their infants were studied by phage typing and drug resistance tests.

Seven of 24 cases showed the same lytic pattern in the strains isolated from the nasal cavity of the newborn and the impetigo lesions of the same babies, but there were only 2 cases in which the strain from the nasal cavity of the mother showed the same pattern as that from the impetigo lesion of their babies. In addition, although they were untypable, there were 3 cases in which there was present the same tendency to resistance for penicillin, streptomycin, and tetracycline in the strains isolated from the impetigo lesions and from the same infant's nasal cavities. These observations show the close relation between the development of the impetigo and the infant's own nasal cavity strain.

Pathogenic staphylococci and the resistant strains were isolated in a high percentage of cases from the nipples of the patients suffering from mastitis and from their infants' nasal cavities. Furthermore, in a large number of patients with mastitis, strains of

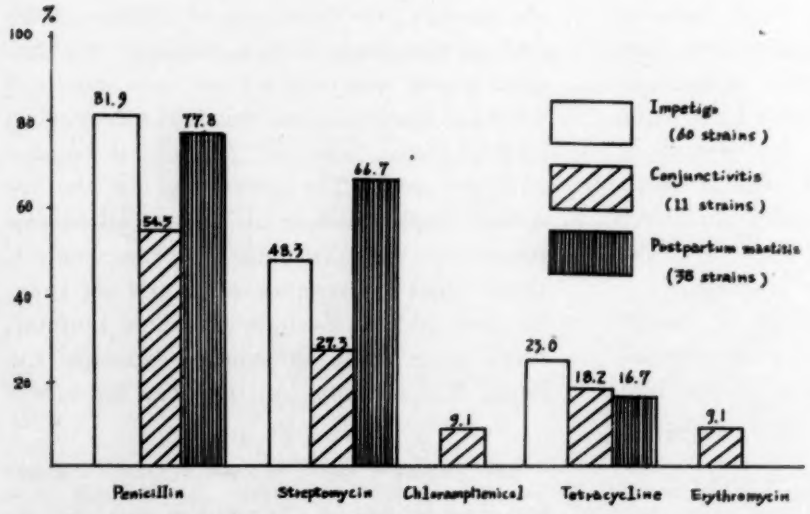

Fig. 2. Drug resistance of staphylococcus isolated from neonatal skin disease and abscess of postpartum mastitis.

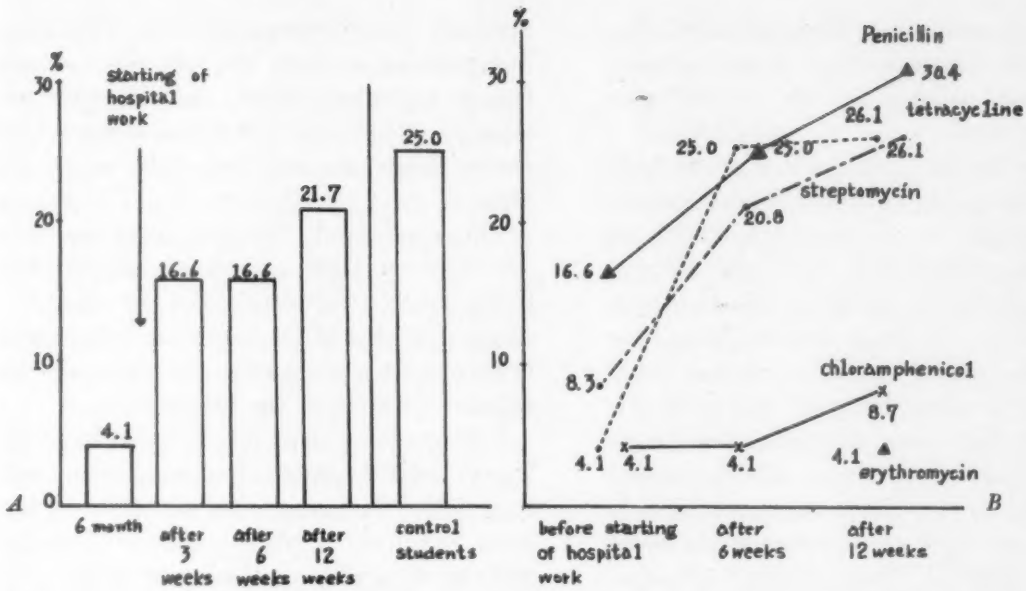

Fig. 3. Frequency of isolation of pathogenic staphylococcus from student nurses at varying times after their coming to work in the hospital *(A)* and change in the percentage of prevalent strains in the same periods *(B)*.

staphylococcus with the same lytic pattern were isolated from nipples, the milk of the mothers, and, at the same time, from the nasal cavities of the infants. The strains isolated from the vagina, however, showed no correlation with those isolated from the lesions of the mastitis. As a source of infection leading to puerperal mastitis, the lochia seems to play no role.

In the study of causative correlation between neonatal impetigo and postpartum mastitis, it was shown that 4 mothers whose infants had impetigo during the hospitalization developed mastitis after going home and in each case strains from mothers and infants showed Group I type.

We can conclude that there is cross infection between the cases of neonatal impetigo and puerperal mastitis which are caused by the staphylococcus existing in the hospital building. We know also that the nasal cavities of the infants and professional workers as well as the fingers of the latter play a major part in the origin of these infections. There were probably many cases which originated in particular members of the professional staff in spite of the fact that we did not have any explosive epidemics of these diseases.

Comment

Several reports[1, 2] have already been made, showing the frequency of antibiotic-resistant staphylococci in the nasal cavities of the hospital staffs and patients in the hospital. Barber and associates[3] have also reported the increased frequency of the carriers of the resistant staphylococcus among mothers and their infants in accordance with

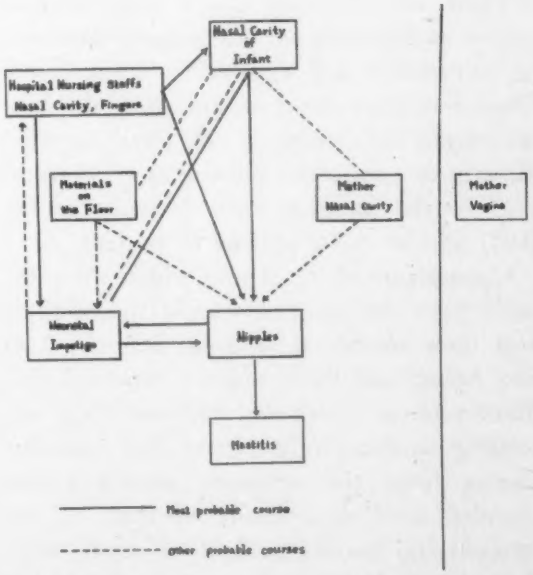

Fig. 4. Course of spread of staphylococcal infection (hypothetical).

the days of postpartum hospitalization. Our own studies of physicians, nurses, student nurses, and patients in the hospital give additional facts.

Patients in the puerperium showed an increase in penicillin-resistant strains cultured from the nasal cavity from 38.9 per cent upon admission to 47.1 per cent at the time of discharge. In newborn infants this tendency was more striking. Two days after birth penicillin-resistant strains could already be cultured from 32.1 per cent, evidence that they were infected in the hospital. Furthermore, newborn infants showed staphylococcus in their nasal cavities in about 90 per cent at the time of discharge from the hospital. These findings are consistent with those in the reports by Muth,[4] Rountree,[5] and Wallmark.[6]

The professional staffs had a higher percentage of resistant strains than the patients in the hospital, namely, for penicillin 48.9 per cent, for streptomycin 23.9 per cent, and for tetracycline 17.0 per cent. It was particularly high among the attending nurses. Student nurses also showed a high percentage of resistant staphylococcus which often appeared after they had started their work in the hospital. These infections were interpreted as being due to a resistant strain, persistent in the hospital.

There are evidently many drug-resistant strains in the hospitals where large amounts of antibiotics are constantly being used. Once a drug-resistant strain enters the hospital from the outside it will infect rapidly, directly or indirectly, passing from hospital staff to the patients, from patients to the staff, and/or from patient to patient.

Comparison of the strains which were isolated from the nasal cavities of the mothers and their infants is of great interest. Loh and Abiog[7] and Saint-Martin[8] reported that there was no correlation between them according to the phage typing, but that the strains from the newborn infants corresponded with those from members of the medical and nursing staffs. Our results were the same, indicating that it was the hospital strain which caused skin disease in the newborn and puerperal mastitis. The causative strains of both diseases were mostly Group I staphylococcus, and, in lytic pattern, 29 and 52 were the most common. Our results from the nursing staffs were the same.

These so-called "hospital staphylococci" are different from ordinary ones in many biological characteristics and in drug resistance. It should be emphasized that some particular strains can be the cause of the massive infection in the hospital.

Scherman[9] reported 69 per cent of staphylococci which caused breast abscess were type 52A/79. Barber and associates[10] isolated 52A from neonatal impetigo; Schaffer and co-workers[11] reported 52, 42B, 47C, and 44A as the causative strains of both lesions. Smith[12] reported 42B, 47C, 44A, 52, 80, and 81 from the same lesions.

There are a number of reports of infections due to phage type 80.[13-16] Rauft-Häussler and associates[17] stated that phage 80 is the hospital strain commonly encountered in the United States, Australia, New Zealand, Sweden, and Germany.

Many studies have been made which have reported the source of infection in neonatal skin disease and postpartum mastitis. In mastitis, the spread of germs from infants to mothers has been emphasized. The route to the infant's nasal cavity has also been frequently discussed and some have stated it was through the air, some, from the attendants. In our study of puerperal mastitis we almost always isolated the same phage type from the nipples and milk and from the nose of the infant. Hence, we came to the conclusion that the nasal cavity of the infants and not the lochia is the origin of the infection of the breast of the mother.

The causative strains of the neonatal impetigo were also found to be either type 29 or 52 of the Group I. These were the predominant types found in mastitis and the same phage staphylococcus was isolated from the nose of the newborn infants and the nursing staffs. Hence, both infant and maternal infections in the puerperium are considered due to the cross infection by the

strains which were present in the hospital. The members of the professional staffs on the floor of these hospitals who are always in contact with patients and their newborn infants in the puerperium are playing an important role in the origin of both diseases. The presumable course of the infection of both diseases is shown in Fig. 4.

For the prevention of the staphylococcal infection of mothers and infants, we should not use antibiotics without strict indications, but, instead, preventive procedures should be more emphasized. In other words, we should improve hygienic conditions. Early diagnosis of the infection and isolation is essential.

Carriers of the organisms should have no contact with the newborn infants. When members of the hospital staff have even superficial infectious lesions, they should not come to work in the hospital.

Conclusions

1. The majority of the skin diseases of newborn infants and cases of postpartum mastitis in our hospital were caused by lytic pattern 29 and 52, Group I staphylococcus. These diseases were due to cross infection in the hospital.

2. Many members of the medical and nursing staffs in the hospital are carrying the same phage type staphylococcus as was cultured in the above diseases. These persons are playing an important role as the carriers of the causative strains and are the source of infection. They are carrying, also, in high percentage, the pathogenic and drug-resistant staphylococus.

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Appendicitis in pregnancy

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THE view is prevalent that appendicitis is a very different and peculiar disease during pregnancy. This study challenges that belief.

Fifty years ago (1911) in the very infancy of appendicitis as a recognized disease, H. H. Schmid[1] made a most thorough study of appendicitis in pregnancy. The first sentence in his paper was: "The subject is not new." He reported 486 instances collected from the literature, and added 23 new cases.

Appendicitis in pregnancy occurs about once in every 1,000 deliveries.[2] It occurs in primiparas (37 per cent) as well as in multiparas (63 per cent). Most writers find a slightly diminished incidence in the third trimester and in labor.[2-5] The well-known elevation of the appendix beginning at the third month of pregnancy[6-8] has been blamed for causing appendicitis. The significance of this is doubtful.[2, 8]

Materials and methods

All instances of appendicitis during pregnancy in the Emanuel Hospital and the Good Samaritan Hospital, Portland, Oregon, were collected and reviewed in order to study the true course of this disease. Of course, our mistakes in diagnosis might be more informative than our triumphs, but an accurate and inclusive survey of these could not be made. Therefore, a series of 59 cases is presented. All of these meet the following criteria:

1. Acute appendicitis was present during pregnancy or parturition.
2. Acute appendicitis was proved by tissue examination of the appendix following operation or at autopsy.
3. The patient was followed until the outcome of pregnancy was determined.

As nearly as possible, this achieves a homogeneous and scientifically valid group of patients with acute appendicitis in pregnancy. All of the records of patients who had an appendectomy during pregnancy were reviewed. This was in itself very informative. Only cases which fit the above criteria were included in this study. An entirely heterogeneous group of surgeons and obstetricians attended these women. The desired information from these charts was transferred to punch cards and analyzed.

Results

An evaluation of the histories of the patients is shown in Table I. Sixty-nine per cent began with generalized abdominal pain, 75 per cent had nausea and vomiting, and 54 per cent had what is considered to be a "textbook" story of appendicitis as described by Cope.[9] Ninety-three per cent of these women had a sharply localized area of abdominal pain. In the later months of pregnancy, this localized pain dutifully moved upward toward the flank in the majority of patients. A vaginal or rectal examination contributed a significant positive diagnostic help in only a few of the cases. This is not to state that these examinations are to be omitted. Their well-established negative value is not measurable in this study.

Most of these patients (76 per cent) had a temperature under 100° F. on admission (Table II). In only 4 patients was it over 102° F. Because the white blood count is

From the Emanuel Hospital and the Good Samaritan Hospital.

slightly elevated during pregnancy, it is not surprising that high white blood cell counts were noted in these patients. Seventy-five per cent of the counts were over 12,000, while 44 per cent were over 16,000. A marked "left shift" was also noted.[10]

In this study, an attempt was made to see how the pregnancies fared under the stress of disease and operation (Table III). Because all of these patients were operated upon, it is not possible to study the effects of untreated appendicitis or medically treated appendicitis. A look at the reports of others, however, suggests that such results are very bad.[1] It was found that 8 or 10 of these pregnancies were interrupted by the disease and operation. The inclusion of the one "therapeutic" abortion and the uncertainty of the effect on a pregnancy 3 days before expected delivery led to this indefinite figure. Thirteen of the patients were judged to have peritonitis and, in 6 of these cases, the pregnancy was terminated. Exploration of the pelvis at operation, the use of drains, treatment with progesterone, the presence of hypotension during operation, and the use of antibiotics were all studied in relation to the interruption of pregnancy (Table IV). None of these factors seemed to be an explanation for interruption.

Six babies did not survive. Only 4 of these deaths could really be attributed to the appendicitis (6.7 per cent) with one premature baby in question. Some discrepancy arises between interruption rate and fetal loss due to near-term disease where termination of the pregnancy by premature labor did not result in fetal loss.

A study of the 6 abnormal babies was also made. There was no connection with the appendicitis in 2 cases. One of these babies had pyloric stenosis and one erythroblastosis. Because fever during gestation has been blamed for fetal maldevelopment, temperature elevation of the mothers was studied, but none of 4 mothers with a high fever (over 102° F.) had an abnormal baby and only one mother of the moderate-fever group.

A most remarkable finding in this study involves the appendectomy wound. Two wounds abscessed; but there were no other wound complications. Even though the incisions were made only a few days before delivery by the normal route; in some instances, neither dehiscence nor hernia was recorded. Half of these wounds were muscle splitting types; the others were through the midline or the rectus muscle vertically. Although 10 cesarean sections were performed in this group of 59 patients (Table V), none was done because of a wound complication.

Table I. Clinical picture of appendicitis in pregnancy (59 patients; 22 primiparas and 37 multiparas)

	Stage of pregnancy				*Total*	
	0-7 weeks	*7-14 weeks*	*Second trimester*	*Third trimester**	*No.*	*%*
Symptoms						
Onset with generalized pain	5	10	15	11	41	69
Nausea and vomiting	5	12	14	13	44	75
"Textbook" picture	4	9	9	10	32	54
Clinical findings						
Generalized right lower quadrant pain	4	8	6	4	22	
Maximum pain at McBurney's point	3	3	7	2	15	
Higher pain point	0	1	3	5	9	
Flank pain	0	0	2	8	10	
Positive help from pelvic-rectal examination	2	2	4	1	9	

*One patient in the third trimester had diarrhea as a symptom. Two cases of appendicitis in the postpartum period are included.

Table II. Temperature and blood counts in appendicitis during pregnancy

	No. of patients
Temperature	
Less than 100° F.	45
100 to 102° F.	10
Over 102° F.	4
White blood count (in thousands per c.mm.)	
Less than 10	5
10-12	8
12-14	10
14-16	8
Over 16	26
Total polymorphonuclear forms (%)	
Less than 60	1
60-70	0
70-80	14
80-90	30
Over 90	12
Band forms (%)	
Less than 10	17
10 to 20	20
Over 20	17

Comment

It appears, therefore, that acute appendicitis in pregnant women is not truly different from appendicitis at other times.[11] The minor differences involve the displacement of the appendix by the enlarging uterus and the elevation of the white blood count which occurs normally in pregnancy. The clinical picture in these patients does not vary more than in a group of nonpregnant women at this age. As usual, awareness of this diagnosis remains the only solution. De Voe and co-workers[11] state: "The greatest dangers lie in attributing abdominal distress to the commonplace complaints referable to the gastrointestinal tract of the pregnant women and in believing the patient to be in labor."

"Treat the disease and leave the pregnancy alone," certainly should be our rule. When appendicitis is diagnosed, operation is indicated. Appendicitis is probably more treacherous during pregnancy than at other times. This is due to: (a) the compounding of many diagnostic pitfalls by the accidents and symptoms of pregnancy; (b) the reluctance of physicians to make and act on such a diagnosis in pregnancy[11]; (c) the uterus being part of any abscess wall. This latter factor involves a diminished ability to localize an infection[12] because of the shift of the small intestine, contraction and shift of the uterus, and the drastic change in pelvic relationships at parturition. When the uterus forms part of an abscess wall, localization is unlikely; abortion is almost inevitable.

There should be no reluctance to operate on these patients. Operation and anesthesia during pregnancy are not likely to cause abortion or premature labor.[3, 12-14] Certainly they are not as likely to interrupt pregnancy as the peritonitis, intoxication, acidosis, and fever which accompany localized or unlocalized appendicitis. Moreover, these wounds

Table III. Outcome of pregnancies

Stage of pregnancy	*Appendicitis with peritonitis*		*Total pregnancies interrupted*	*Total babies lost*	*Abnormal babies*	*Total in this stage*
	To term	*Interrupted*				
0-7 weeks	0	1	2	2	0	7
7-14 weeks	2	1*	1*	1	2	13
Second trimester	3	1	1	1	3	20
Third trimester	1	4	6 (or 5)†	2	1	17
Post partum	—	—	—	—	—	2
Total	6	7	10 (or 8)†	6‡	6§	59

*Therapeutic abortion.

†Some patients with appendicitis were so close to term that it was difficult to fix it as a cause for onset of labor.

‡One death was due to prematurity; one to cephalopelvic disproportion.

§One baby had pyloric stenosis, one had erythroblastosis; thus only 4 were truly developmental. Of patients with temperature over 102—no abnormal babies; with temperature over 100—one abnormal baby was noted.

Table IV. Various factors in connection with interrupted pregnancies

Factors	*No. of interrupted pregnancies*	*Total No. of patients*
Duration of symptoms of appendicitis to diagnosis (in hours)		
< 24	1	23
24 to 48	4	12
49 to 72	1	6
> 72	4	5
Progesterone administered	3	14
Pelvic organs explored during operation	3	9
Drains used in peritoneal cavity (any location)	4	7
Antibiotics given	8	33
No antibiotics given	2	26
"Shock" present (blood pressure 80 or less for any period)	0	4

seem to cause no trouble at time of delivery.

The problem patients are those in labor, or, as so often happens, those who develop appendicitis with peritonitis at term. The single maternal death in this series occurred at this time. The real problem at such a critical time is to make the diagnosis. Once in this series, appendicitis was diagnosed and confirmed during labor.* In 2 unusual cases acute appendicitis was accidently discovered at cesarean section of women thought to be in labor. At this time, peritonitis should be treated with antibiotics, decompression, fluid balance, and removal of the diseased appendix. It is unlikely during labor, established or imminent, that localization and abscess formation and limited drainage can be dependable. It also appears that labor may progress normally after appendectomy[5, 15]; therefore, we should wait for labor to begin. Cesarean section should await the standard indications for that operation. A real dilemma may arise when peritonitis is accompanied by fetal distress. If cesarean section is done, a low extraperitoneal operation should be performed to avoid contamination of the uterine cavity. Fetal distress may contraindicate this operation which takes longer than a classical cesarean. Renn and others[4] propose six different methods of handling appendicitis at term: (1) appendectomy alone with spontaneous delivery; (2) low cervical section with appendectomy; (3) hysterectomy and appendectomy; (4) appendectomy with manual dilatation and vaginal delivery; (5) extraperitoneal section followed by appendectomy via separate incision; (6) appendectomy with induction of labor. Surely most of these are far too radical. It seems that a logical plan at term would be to treat the appendicitis and peritonitis, and await developments. Only fetal distress should call for intervention; low cervical or extraperitoneal section should then be done.

One must be prepared to face the added difficulty in diagnosis of appendicitis during pregnancy. To the many usual complaints which suggest appendicitis will be added most of the complications of pregnancy. A larger percentage of error is inevitable,[2, 10, 12, 16, 17] over 50 per cent in some series. In late pregnancy, pyelonephritis is the most common complication and may be an almost exact imitator of appendicitis. Ectopic pregnancy is the pitfall in early months. An especial danger also is to mistake the onset of abortion or labor for appendicitis. Unlikely though this may seem, it was noted often in this study. When the appendix proved normal and the abortion proceeded, the surgeon was indeed embarrassed.

Table V. Maternal statistics

Maternal deaths	1	(post partum)
Maternal complications	10	(only 2 were due to appendicitis)
Cesarean sections	10	(in only 3 did appendicitis occur close to term and influence the indications)
Incisions		
Muscle splitting	30	
Vertical	29	
Dehiscences	0	
Wound abscesses	2	

*Dr. Louise Clancy.

Summary

A consecutive series of 59 cases of proved acute appendicitis in pregnancy has been presented. Study of the records of these patients suggests that their disease was in no significant way different from appendicitis in the nonpregnant state. Operation did not harm these patients or their babies. It was of great benefit, because it saved many from the hazards of advanced appendicitis.

At term and in labor the special problem of appendicitis involves not only added difficulty of diagnosis, but a simultaneous decision regarding 2 conditions and 2 people. It appears that operation for the appendicitis or peritonitis and careful conservatism toward the pregnancy constitute the best solution.

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Urachal cyst abscess

Report of a case

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INTRAPERITONEAL perforation of a urachal cyst abscess is an unusual cause of an acute abdominal crisis. To date there have been no reports of such a complication of pregnancy or of the immediate postpartal period.

Only two reports of urachal abnormalities associated with the gravid state have been published. Callanan[1] described the chance finding of a noninfected urachal cyst at hysterotomy performed for missed abortion and Sterling and Goldsmith[2] related the onset of a discharge from the umbilicus after delivery, a discharge which persisted for 8 years until it was cured by excision of an infected urachal sinus.

An 18-year-old pregnant woman who had given birth to one child and whose last menstrual period was Jan. 9, 1958, was admitted to the hospital on Oct. 11, 1958, complaining of dysuria and pelvic discomfort of 2 weeks' duration. The pregnancy had been uneventful. The estimated date of confinement was Oct. 16, 1958. The patient said that a right inguinal hernia had been repaired in 1956 and that a normal pregnancy had ended with the delivery of a full-term female infant in the same year.

We found the abdomen to be soft and not tender; the uterus was somewhat small for the estimated 39 weeks' gestation, with vertex presentation of the fetus. The fetal heart tones were normal. Rectal examination showed the vertex to be at the plus-1 station. The cervix was dilated 2 cm. and was almost completely effaced. Occasional uterine contractions were noted but they caused no discomfort to the patient. Results of urinalysis and of Gram's staining of urinary sediment were normal. Mild sedation was administered and, with rest in bed the patient's symptoms subsided completely within 24 hours and she was dismissed.

The patient was admitted a second time 4 days later. She was in active labor which proceeded uneventfully to the spontaneous delivery of a living female infant, 7 pounds and 2 ounces, over an intact perineum. The total estimated loss of blood was 25 c.c. The patient was returned to her room in good condition.

On the fourth postpartal day her temperature increased to 101.4° F. She complained only of dysuria, and results of a general examination were considered normal in view of her postpartal stage. One examiner did palpate a fibrous band between the umbilicus and the symphysis pubis. This band was not particularly tender. It was thought perhaps to represent a urachal remnant. A specimen of urine obtained by catheter contained only a few erythrocytes, and culture of urinary sediment produced no organisms.

The patient had remained afebrile for 24 hours, when the temperature increased precipitously to 103° F., and severe pain in the epigastrium arose suddenly, followed by generalized abdominal pain. Mild rebound tenderness was noted over the abdomen, being more pro-

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The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

nounced over the uterus. The lochia was normal in amount and appearance. Results of another urinalysis were not significant. Penicillin, streptomycin, and analgesic agents were administered for what was thought to be parametritis.

The next morning the temperature remained elevated and the abdominal pain had increased. Rebound tenderness was most marked over the lower abdominal quadrants. Bowel sounds were absent. The value for hemoglobin was 14 Gm. per 100 c.c. of blood; leukocytes numbered 12,900 per cubic millimeter of blood; the value for serum amylase was less than 160 units. A roentgenogram of the thorax showed no free air under the diaphragm and was otherwise of no significance. A flat roentgenogram of the abdomen revealed gas-distended loops of small and large bowel, without fluid levels. Surgical consultation was requested and abdominal surgical exploration was advised on the basis of peritonitis of indeterminate origin.

Operation was performed by one of us (Symmonds), and the notes follow:

"A primary right rectus muscle retracting incision was made just to the right of the umbilicus. There was approximately 1,500 c.c. of purulent fluid in the abdominal cavity with considerable exudate over all the peritoneal surfaces. A complete exploration with visualization of the stomach, duodenum, gall bladder, pancreas, the entire small bowel, appendix, and the entire colon was made without finding any apparent source for the peritonitis. The uterus and adnexa were intact and normal in appearance. Eventually a 1 cm. hole in the parietal peritoneum of the lower abdominal wall, halfway between the umbilicus and the dome of the bladder, was discovered" (Fig. 1). "The opening was found to enter a 6 × 4 × 4 cm. abscess cavity within the abdominal wall. The incision was lengthened and the abscess entered. It was found to connect with but did not appear to communicate with the dome of the bladder by the urachus. The urachus was excised from the top of the bladder and the defect closed with two rows of continuous No. 2-0 chromic catgut and a third row of interrupted sutures. The entire urachus cyst-abscess was excised following which the peritoneum was closed with continuous sutures of No. 1 chromic catgut. Through-and-through tension sutures of nylon were inserted, and the skin closed with interrupted sutures of black silk. A single Penrose drain was led down to the area of the abscess and to the dome of the bladder."

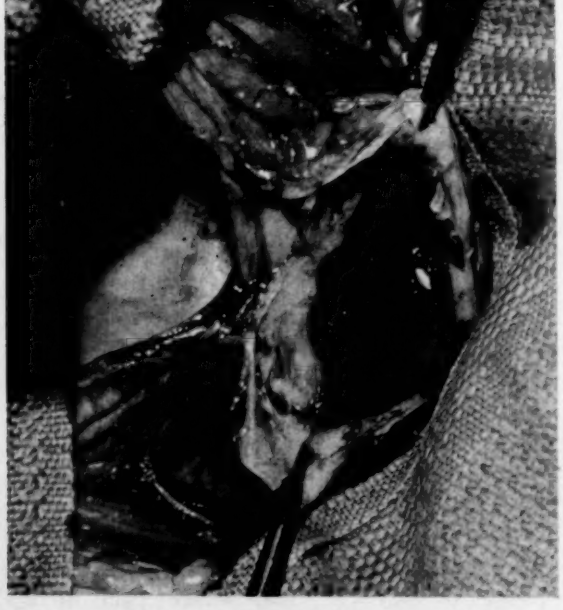

Fig. 1. Postpartal uterus visible beneath peritoneal opening on the left. The opening of the urachal cyst-abscess is on the right. The patient's head would be to the left.

Fig. 2. Operative specimen; a probe extends through the urachus. The cyst was attached to but did not communicate with the bladder proper.

The pathologist's report described a collapsed, infected urachal cyst forming a mass 6 cm. in diameter. A narrow opening into the urinary bladder would just admit a small silver probe (Fig. 2).

The patient's temperature remained less than 99.6° F. throughout the postoperative period and she was dismissed from the hospital on the tenth day after the operation.

She was again seen a year later, at which time

she complained of lower abdominal pain. In the course of investigation at this time urinalysis, urography, and cystoscopic examinations were performed, all of which gave negative results.

Comment

The urachus is the embryologic remnant of the upper end of the ventral cloaca which forms the bladder,[3] or it represents the residuum of the allantois.[4] Long[5] classified urachal abnormalities as follows: a tract opening into the bladder, the umbilicus, or communicating with both, or midline cysts without communication to the bladder or skin. The latter are the most common and they usually remain undetected unless they become infected. When infection arises lower abdominal pain, a midline mass, and fever become apparent. The infected cyst or abscess may remain relatively quiescent for years, with repeated exacerbations,[6] or it may rupture through the umbilicus or into the bladder, bowel, or peritoneal cavity, as was noted in our case. It could not be determined whether or not delivery had been assisted by external abdominal pressure which could have resulted in the intraperitoneal rupture of the abscess.

The mechanism of infection is not known, but infection is variously regarded as taking place by way of the bladder, the blood, or the lymphatic system. Thompson[7] wrote that frequently a low-grade infection is present in the extraperitoneal fascia in which the urachal remnants lie.

Drainage and curettage of the acutely infected cyst-abscess, followed at a later date by excision, if a sinus persists, are considered by most observers to be the safest surgical treatment. However, when the cyst has perforated into the peritoneal cavity, primary excision of the cyst with closure of the defects in the bladder or bowel, if defects have developed, is the treatment of choice.

Summary

An unusual case of intraperitoneal perforation of a urachal cyst-abscess with generalized peritonitis complicating the postpartal period has been reported and a brief discussion of the problem has been presented.

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Vascular lesions of the posterior fossa during pregnancy

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VASCULAR lesions of the posterior fossa during pregnancy are apparently rare. Only sporadic cases have been found in the literature, and these were diagnosed at autopsy.[3, 5]

This paper consists of data obtained from 2 patients who were observed at the University of Mississippi Medical Center during the fall of 1959.

Case reports

Case 1. B. B. J., a 27-year-old Negro woman, was admitted to the University Hospital on Oct. 30, 1959. She had had severe nausea and vomiting during the first trimester of pregnancy, 24 months previous to the present illness. Despite this complication, the pregnancy ended in spontaneous delivery without difficulty. The patient did well until the present pregnancy.

The present illness started during the first trimester of pregnancy with symptoms of nausea and vomiting. These symptoms were so severe that she required two days' hospitalization. After intravenous fluids and chlorpromazine were administered, the nausea and vomiting ceased.

Although clinic appointments were made, the patient was not seen again until the fifth month of pregnancy at which time she complained of headache, vomiting, weakness, "dizzy spells," and staggering. These symptoms had become progressively worse over the previous three weeks. Examination demonstrated a chronically ill, emaciated Negro woman who was drowsy with normal vital signs. The optic disc margins were blurred and there were bilateral retinal hemorrhages. She had a slight suggestion of left peripheral facial palsy. The deep tendon reflexes were hyperactive. The patient's gait was staggering with a broad base and the Romberg sign was positive. The fundus of the uterus was found to be 1 cm. above the umbilicus and the fetus could be outlined. Diagnoses on admission were (1) hyperemesis gravidarum; (2) malnutrition, secondary to hyperemesis; and (3) optic neuritis. It was felt, however, that a brain tumor should be ruled out. The cerebrospinal fluid pressure was 400 mm. The fluid was clear and colorless. Bilateral carotid arteriograms were normal.

A Pantopaque ventriculogram demonstrated distortion of the aqueduct and a filling defect on the left side of the fourth ventricle (Fig. 1). A suboccipital craniectomy revealed a milky-colored dura over the left cerebellar hemisphere. The dura was tense and not pulsating. Beneath the dura, directly over the left cerebellar tonsil, was a well-encapsulated 2 by 4 cm. mass surrounded by multiple small cysts. The mass was entirely enucleated.

Microscopic sections (Fig. 2) demonstrated a hemangioendothelioma (hemangioblastoma of Cushing and Bailey). The patient's postoperative course was entirely benign and she was discharged from the hospital on the thirteenth postoperative day with her pregnancy undisturbed.

The patient was readmitted to the hospital 3½ months following operation and delivered a 7 pound, 15½ ounce female infant. The mother and child were discharged from the hospital perfectly well.

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Case 2. S. L. S., a 17-year-old white gravida i, was observed in the Emergency Room of the University Hospital for the first time on Nov. 16, 1959. The patient had been semicomatose and in respiratory distress for 8 hours. She was known to be 7 months pregnant and she had been well until the morning of admission, at which time she was awakened by a severe headache. Within one hour she became unresponsive. A lumbar puncture yielded grossly bloody cerebrospinal fluid. A tracheotomy was performed and the patient was transferred to the University Hospital, a distance of some 150 miles. In the Emergency Room, she responded to painful stimuli by decerebrate movements in the left upper extremity, alternate decerebrate and purposeful movements in the right upper extremity, and by withdrawal in both lower extremities. The pupils were equal at 3 mm. and reacted to light. Funduscopic examination was normal. The neck was supple. The deep tendon reflexes were bilaterally hyperactive. The plantar reflexes were down bilaterally. The fundus of the uterus was above the umbilicus and the fetal heart tones were normal. The possibility of a ruptured aneurysm or angioma was considered. Carotid arteriograms were normal.

A vertebral arteriogram (Fig. 3) demonstrated upward displacement of the superior cerebellar arteries and an anomalous vessel in the left cerebellar hemisphere. On the x-ray table, the patient became decerebrate throughout. She was taken immediately to the operating room. Spontaneous respirations ceased. Artificial respiration was instituted and a suboccipital craniectomy rapidly performed. A 20 to 30 c.c. hematoma was evacuated from the left cerebellar hemisphere. An anomalous vessel beneath the hematoma was coagulated.

Twelve hours following operation, the decerebration was less; but she had developed bilateral pulmonary edema, a temperature of 103° F., and a fall in blood pressure from 120/80 to 85/75. She was treated with penicillin, chloramphenicol, digitoxin, hydrocortisone, levarterenol, and positive pressure oxygen. Despite these measures, the fetal heartbeat became inaudible about 18 hours following operation; and the patient was spontaneously delivered of a stillborn infant about 48 hours after operation.

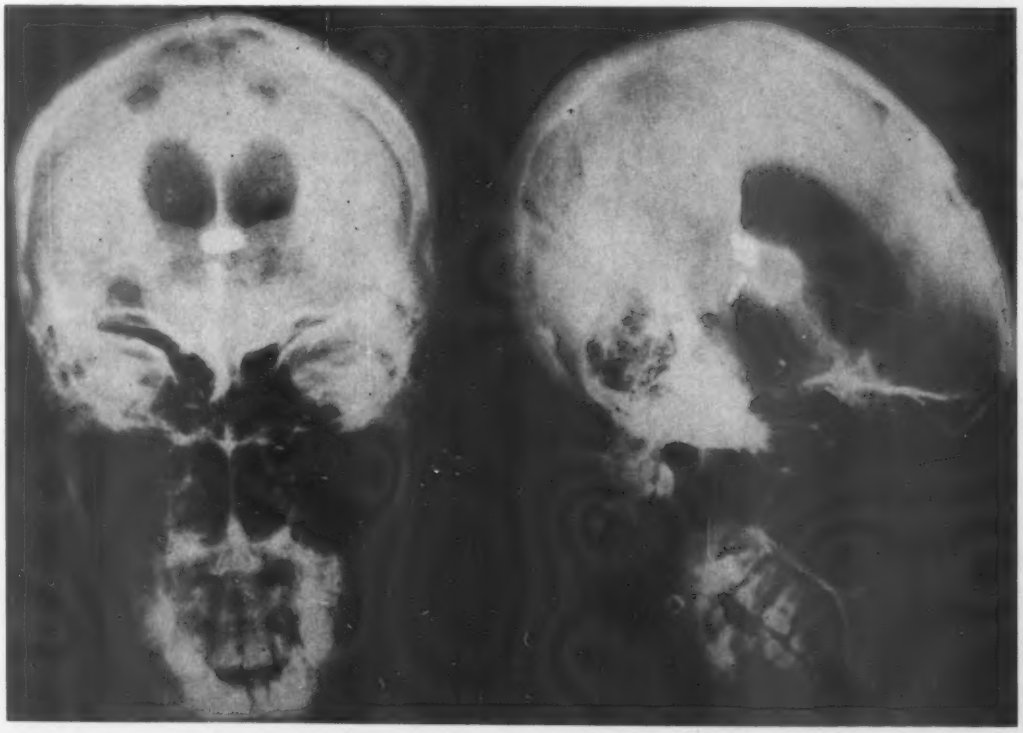

Fig. 1. Case 1. Air and pantopaque ventriculogram. Note the large lateral ventricles filled with air; the wide third ventricle with shift of the aqueduct from the left to right in the anteroposterior view. The fourth ventricle is shifted to the right. A small amount of opaque medium can be seen in the subarachnoid space. On the lateral view, note the almost perpendicular position of the aqueduct of Sylvius.

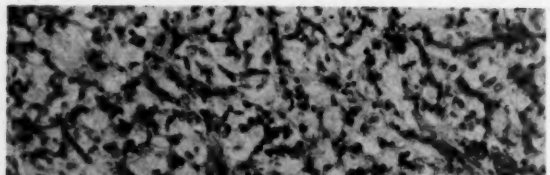

Fig. 2. Case 1. Photomicrograph of mass excised showing numerous capillaries lined by foamy, plump, polygonal cells. (Hematoxylin and eosin. ×100.)

After delivery, she was much more responsive. She gradually began walking, talking, and feeding herself, and was discharged from the hospital three weeks postoperatively.

She was readmitted on June 27, 1960, at which time she was coherent, fed and dressed herself, and walked with a moderate ataxia. The only positive neurological findings were poor coordination on the left and hyperactive reflexes throughout with unsustained clonus. Repeat arteriograms demonstrated a 1 cm. segment of the previously noted anomalous vessel still present.

Comment

The incidence of vascular lesions in the posterior fossa during pregnancy is not known, although it is thought to be rare. Rand[5] in 1955 reported a total of 41 cases of brain tumors and related lesions in the course of pregnancy which were taken from his experience and from a review of the literature. Seven of these were lesions of the posterior fossa. None of them could be basically classed as a vascular tumor, except a case of hemangioblastoma reported by Duperrat[3] in 1945 in the French literature. Rand[5] also reported 34 cases of subarachnoid hemorrhage which were taken from his experience and from the literature. One was an angioma of the posterior fossa in a patient who died in the sixth month of pregnancy.

Cushing and Bailey[2] in 1928 referred to a case of a young housewife with precipitating signs of increased intracranial pressure in the course of pregnancy which were ascribed to toxemia. Pregnancy was interrupted at the eighth month, but the symptoms persisted and failing vision ensued. Three months later, a brain tumor was suspected; and at the operation, this proved to be a midcerebellar cystic hemangioma. Cushing[2] commented: "Pregnancy appears to be a not uncommon provocative element in bringing tumors to light, more particularly perhaps angiomatous lesions."

It is a general belief that pregnancy actually stimulates the growth of tumors, but the etiological factors related to the symptoms of vascular lesions of the central nervous system during pregnancy are poorly understood. Cases of parasellar meningiomas with repeated exacerbations and remissions during and after pregnancy, respectively, have been reported by several writers.[1, 5, 6] It is their belief that the tumor cell volume enlarges during the course of pregnancy, thus causing an enlargement of the mass itself. King[4] suggests that "vascular engorgement" would be the most likely explanation, it being related to the increased blood volume. All agree that the change is most marked during the latter months of pregnancy when estrogen and progesterone levels are at their peak and water retention greatest.

In spontaneous subarachnoid hemorrhage, Rand's[5] personal cases were all in the latter four months of pregnancy or in the early postpartum period. Of the cases he obtained from the literature, one patient hemorrhaged in the third and fifth months; but this patient had had a previous hemorrhage prior to her pregnancy. Another patient hemorrhaged in the fourth month, and the remaining patients were in the last four months of pregnancy. From this we can see that, if symptoms of an intracranial hemorrhage or a mass lesion occur, they will be more common in the last half of pregnancy and most likely to appear in the last trimester.

These factors would certainly lead one to feel that there is a strain on the intracranial vascular system during the latter trimester of pregnancy. It remains to be proved whether the strain is due to direct action on blood

vessels by hormones, increased blood volume, or water retention.

The differential diagnosis of vascular lesions and/or tumors in the intracranial cavity during pregnancy may be quite difficult. In the first patient of this report, symptoms were similar to her previous known episodes of nausea and vomiting during pregnancy. Her headaches and eyeground changes led to a lumbar puncture which demonstrated a markedly elevated cerebrospinal fluid pressure. The differential diagnosis in the second patient, who had massive subarachnoid hemorrhage, was not as difficult. Obviously, a catastrophe had occurred. Localization of the lesion was supported by the presence of small pupils which reacted readily to light associated with obvious decerebration. It is of interest to note that a sibling of this patient has a known Sturge-Weber syndrome.

The question as to the proper time for surgical intervention in pregnant patients with brain tumors and subarachnoid hemorrhages varies with the problem at hand. One must keep in mind that in each case there are two lives to be considered. Irradiation may be considered a hazard in the case of diagnostic studies. In these patients, we routinely shield the patient's abdomen in order to protect the fetus and continue with the diagnostic studies as indicated. We feel that in both of the present cases neither mother nor infant would have survived had therapy not been instituted during the course of pregnancy. The condition of the first patient was progressively deteriorating when she was seen. The precarious state of the second patient was obvious from her progressive decerebration and cessation of spontaneous respiration. The loss of the fetus in the second case was considered to be associated with an episode of hypoxia which occurred 12 to 16 hours postoperatively. The hypoxia was thought to be due to pulmonary edema precipitated by aspiration pneumonia.

Fortunately, intracerebellar lesions, once

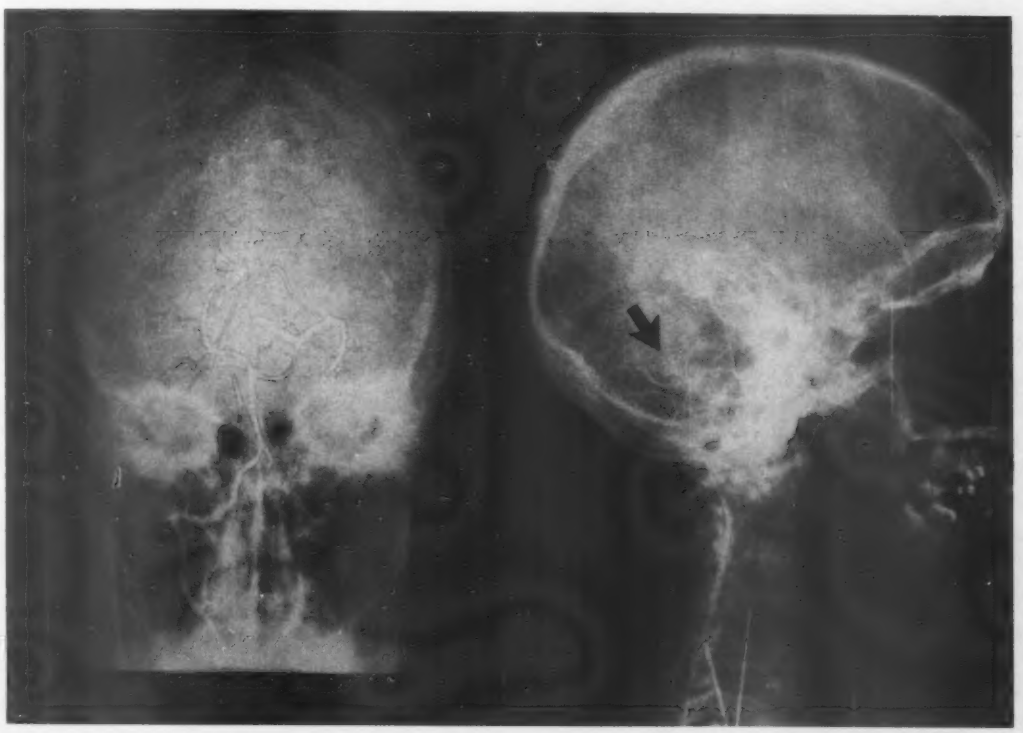

Fig. 3. Case 2. Vertebral arteriogram, anteroposterior and lateral views (retouched). Note large anomalous vessel to left of basilar artery. This is again demonstrated on the lateral, running a horizontal course through posterior fossa from an angioma (at tip of the arrow). Superior cerebellar artery and posterior cerebral arteries are noted to be stretched and elevated in the midportion of their course on the lateral view.

cured, leave very little in the way of neurological deficit. The first patient had none. We feel that this case may represent a cure, since intact, enucleated hemangioblastomas rarely recur. The second patient is recovering more slowly but is presently able to get along well in society and care for herself. Since her lesion is an angioma, a follow-up vertebral angiography was done. The residual lesion was felt to be insignificant.

Summary and conclusions

In summary, vascular lesions and intracranial tumors should be strongly considered in the differential diagnosis when headaches, nausea, and vomiting occur during the latter months of pregnancy. We feel that diagnostic studies and intracranial surgery may safely be done during pregnancy to the advantage of both mother and infant.

Two cases of vascular lesions of the posterior fossa diagnosed and successfully treated in the course of pregnancy were reported. The writers believe that in each case of pregnancy, if symptoms of intracranial pressure appear, these should be carefully evaluated. If a lesion is proved, it can be removed with a reasonable probability of success even if it is located in the posterior fossa.

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Hemorrhage from rupture of the pelvic veins complicating pregnancy

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MASSIVE intra-abdominal bleeding from rupture of the uteroovarian or ovarian vessels during pregnancy is a rare but dramatic, frequently puzzling, and often fatal complication in obstetrics. Scant attention is given to this type of emergency in the standard textbooks of obstetric practice. It is a distinct challenge to the ability of the clinician in both diagnosis and management. Indecision and delay account for the high mortality of almost 50 per cent.[1] It is felt that a number of these cases continue to occur unrecognized as the cause of unexplained maternal deaths.

It is the intent of this paper to review the literature to date and add 2 cases from the private practice of the author. It is hoped that by emphasizing the occasional importance of this complication it can be kept in the mind of the clinician. The correct diagnosis and indicated energetic treatment is forthcoming only if this possibility is kept in mind.

In 1904 Williams[2] first reviewed the literature on hemorrhage from the uteroovarian veins as a complication of pregnancy, citing 31 previously reported cases and adding one of his own. He noted the first recorded case as one observed by Baudelocque in 1778.

Samuelssen[3] in 1954 reported 47 cases, including one of his own, in minute detail. The greatest number of cases, however, was collected by Hodgkinson and Christensen[1] in 1950. They reported, though not in detail, 72 cases and added 3 of their own. The mortality in their collected cases was 49.3 per cent.

Six additional examples have found their way into the literature since the article by Hodgkinson and Christensen, one each by Menaker and Cauble[4] in 1953, Conger and Paternite[5] in 1954, Millet, McKenna, and Shell[6] in 1956, Charles[7] in 1957, Hill and Darling[8] in 1958, and Diddle, O'Connor, and Platt[9] in 1958.

This author's 2 cases both occurred in 1958, one month apart.

From St. Peter Hospital.

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Case reports

Case 1. A. S., a 23-year-old white primigravida, was first seen on Oct. 1, 1957, and gave August 18 as the date of her last menstrual period. The estimated date of confinement was May 25, 1958. The initial examination revealed a gravid uterus consistent with the period of amenorrhea and a 10 cm. doughy, tender, freely movable mass lying to the right of the uterus. The clinical impression was dermoid cyst of the right ovary and early pregnancy. No symptoms attributable to the cyst could be elicited.

On the day after Christmas, when the patient had reached the second trimester, laparotomy was carried out. The uterus appeared normally consistent with a 4 months' pregnancy. The right ovary was replaced by a doughy cystic mass measuring about 14 cm. in diameter and attached to the broad ligament by a narrow pedicle. No varicosities were noted in the operative report. There were no adhesions involving this mass, and it was brought into the incision with little trauma to the pelvis in general. The pedicle was secured with a suture ligature of

No. 0 chromic catgut. Bleeding was almost entirely absent. The abdomen was closed without appendectomy or other disturbance to the pregnancy. The patient made an uneventful recovery. The pathologic diagnosis was pseudomucinous cystadenoma of the ovary.

On January 25, one month later, the patient was seen in the office because of sudden onset of acute right lower quadrant pain associated with nausea. The temperature was 99° F., and the white blood count 18,300 with 87 per cent polymorphonuclear neutrophils. The hemoglobin level was 10.6 Gm. per cent with a hematocrit determination of 33. The urine was clear. Physical findings were limited to marked tenderness in the right lower quadrant and mild rigidity. The pulse was 96 and the blood pressure 110/58. With a diagnosis of acute appendicitis the patient was rushed to the operating room and the abdomen re-entered through the previous incision. The peritoneal cavity contained fresh blood and clots in excess of 1,000 c.c. The bleeding site was quickly and easily identified on the posterior aspect of the right infundibulopelvic ligament at least 4 cm. lateral to the stump of the ovarian pedicle, which still after 4 weeks contained intact the suture ligature from the previous operation. There was no extravasation of blood beneath the peritoneal surface. The peritoneum between the ligature and the bleeding site was smooth and without evidence of adhesions. Numerous vermiform dilatations of the vessels were visible between the uterus and right pelvic wall. Suture ligature controlled the bleeding and the patient received 1,500 c.c. of whole blood. An uneventful recovery followed. Shoulder pain in retrospect was denied by the patient.

The remainder of the pregnancy progressed smoothly and the patient was delivered uneventfully on May 28.

Case 2. P. E., a 35-year-old white primigravida with long-standing infertility, was first seen on July 27, 1957. Her last menstrual period was given as June 10 and the estimated date of confinement March 17. The initial examination confirmed the pregnancy with a 5 cm. soft, cystic, freely movable and nontender mass in the region of the right ovary. All other findings including the laboratory studies were within normal limits. The pregnancy progressed without incident. The right adnexal mass decreased in size and on October 19 was no longer palpable. The fetus on January 10 and January 31 was noted to lie in a transverse presentation. On January 31 the hemoglobin concentration was 12.4 Gm. per cent with a hematocrit determination of 36.

In the late evening of February 7 the patient noted the sudden onset of suprapubic pain spreading rapidly to include the entire abdomen. She could not stand or walk and was brought to the hospital by ambulance. There was some nausea but no vomiting. She denied shoulder pain at all times before operation. The temperature was normal, pulse 88, and blood pressure 100/60. The patient appeared acutely ill and apprehensive. There was no vaginal bleeding. The abdomen was generally tender but without marked rigidity. The uterus was soft with the fetus in a right occipitoanterior position with the head high and the fetal heart tones of good quality in the right lower quadrant. The initial clinical impression was placental abruption. Considered also were torsion or rupture of the right adnexal cyst palpated at the initial office visit, ruptured uterus, abdominal pregnancy, and hemorrhage from varicose pelvic veins. A flat plate of the abdomen confirmed the intrauterine position of the fetus and the absence of a placental shadow suggested the possibility of placenta previa. The hemoglobin level was 9.5 Gm. per cent and hematocrit determination 27, quite a contrast to the hemogram one week earlier. This finding strongly indicated a diagnosis compatible with blood loss. The fibrinogen level was normal.

The lack of development of uterine hardening and the continued well-being of the fetus mitigated against a diagnosis of intrauterine bleeding. The patient was taken to the operating room with a diagnosis of extrauterine hemorrhage. When the peritoneal cavity was opened fresh blood and clots estimated to be in excess of 1,500 c.c. were found. The wide distribution of this blood gave no clue as to its source. Exploration for the site of bleeding was impossible until a low cervical section had been carried out, which incidentally disclosed a complete placenta previa. The bleeding was finally located in a grapelike cluster of huge varicosities on the posterior surface of the left broad ligament close to the uterus. There was little subperitoneal extravasation of the blood. The loss of blood was promptly controlled with a No. 0 chromic suture ligature. No pathologic condition was obvious in the right adnexa, the site of the small mass palpated on the first office visit. The

baby cried immediately, weighed 5 pounds, 5 ounces and did well. The mother made an uneventful recovery after having received 2,000 c.c. of whole blood.

One might criticize the inclusion of the first case in this report on the basis of the prior operation. Its inclusion, however, seems logical and warranted in consideration of the following facts: (1) the 4 week time lapse between oophorectomy and hemorrhage, (2) the absence of subperitoneal extravasation of blood, (3) the distance between the still intact suture ligature and bleeding site, (4) the lack of peritoneal defect or evidence of adhesion, and (5) the presence of varicosities. No doubt the pre-existing pathologic condition as well as the pregnancy contributed to the varicosities.

The absence of shoulder pain in both cases is noteworthy. Diagnostic difficulties are simplified by the presence of this mainstay to the diagnosis of intraperitoneal bleeding.

Comment

Hemorrhage from the ovarian or uteroovarian veins complicating pregnancy can be classified, first, as to whether it occurs during pregnancy or occurs associated with or following labor and, second, as to whether it results in intraperitoneal bleeding only or results in retroperitoneal hematoma formation with or without secondary spill into the peritoneal cavity. Of the 83 cases reported to date 35 or 42 per cent occurred before the onset of labor, with a mortality rate of 28 per cent. A much higher mortality rate follows this complication when associated with labor since the diagnostic problem is much more quandrous.

Intraperitoneal hemorrhage alone is more often found when this complication arises before the onset of labor. Conversely, the hematoma type of hemorrhage more often occurs during or following labor.

The earliest case was noted at 10 weeks' gestation, the latest 21 days post partum.[3] The diagnosis should be considered in all cases of unexplained shock complicating pregnancy, labor, or the early puerperium.

Etiology

The cause of rupture of the ovarian or uteroovarian vein during pregnancy is speculative. Most operators have noted the presence of unusually marked varicose changes in the vicinity of the hemorrhage site. Ectasia of the pelvic veins during pregnancy is a common observation of all surgeons doing cesarean sections. Burwell[10] in 1938 demonstrated that the pressure in the uterine vein during pregnancy is two to three times higher than in the nonpregnant state. He further showed that this increase in venous pressure is not due to increased intra-abdominal pressure and could only partially be explained by the weight of the gravid uterus on the pelvic vessels. The venous pressure however is more widely influenced by posture, muscular activity, respiratory efforts, etc., during pregnancy than in the nonpregnant state.

Hodgkinson[11] in 1953 concluded, after his detailed studies of the physiology of the ovarian veins in pregnancy, that the capacity of these veins increases sixtyfold by the thirty-sixth week and that the tension of their walls increases two and a half times. Hypertrophy of the elastic lamina of the vessel wall apparently facilitates this change.

Samuelssen[3] cited the work of Vignes who studied histologically the changes in the ovarian veins during pregnancy. He noted atrophy of the muscular coat of the vessel with connective tissue replacement. Incomplete regression during the postpartum period leads to progressive fragility of the veins with each additional pregnancy. Eighty per cent of the collected cases of hemorrhage studied were in multiparas. Notkovich[12] in 1956 pointed out the occasional association of this bleeding complication of pregnancy with an anomalous pattern of the ovarian-renal vascular systems. In final analysis, however, it is impossible to state whether or not hemorrhage is related to these physiologic changes in the pelvic vessels or to some less obvious superimposed pathologic change.

Nearly all writers give careful consideration to the part played by trauma in the

etiology of hemorrhage from the pelvic veins during pregnancy. The presence of such trauma, of course, is quite obvious in those cases occurring during active labor. Much more subtle, however, is the part played by trauma in the hemorrhages occurring unrelated to labor. Some form of stress seems to have been an important contributing factor to the onset in 50 per cent of the cases in this latter category. The most common forms of muscular activity are straining at stool, lifting an older child, lifting or moving household furniture, coitus, coughing, etc. In neither of the cases detailed in this presentation could any initiating stress factor be elicited.

Diagnosis

The diagnostic symptoms and signs differ widely with the type of bleeding encountered. Pain of acute and sudden onset is the universal symptom. This is usually rapidly followed by shock. If the hemorrhage is confined to the retroperitoneal space, the pain and tenderness is first localized in either the right or left lower quadrant or flank. Signs and symptoms of general peritoneal irritation develop later and more slowly. If bleeding takes place directly into the peritoneal cavity, the symptoms are those common to hemoperitoneum—general abdominal pain, nausea, vomiting, and shoulder pain. Prominent findings are general abdominal tenderness, distention, absent bowel sounds, and shifting dullness. The uterus is soft in contrast to its increased tone in placental abruption and the fetal heart tones remain of good quality unless shock has progressed to fetal anoxia. The hemogram usually reveals leukocytosis with a shift to the left, accompanied by anemia.

If this complication occurs during labor, the signs and symptoms are frequently obscured and progressive unexplained shock may be the only evidence that something is amiss.

The differential diagnosis during pregnancy includes ectopic gestation, abruptio placentae, ruptured uterus, adnexal torsion, ruptured pelvic cyst, appendicitis, renal pathology, and hemorrhage from liver, spleen, or other abdominal organs. During or after labor the differential diagnosis includes ruptured uterus or other pelvic trauma and torsion or infarction of a pelvic tumor during involution.

Treatment

Once the diagnosis is considered possible the treatment becomes obvious. Immediate steps should be taken to combat shock in preparation for operation. An adequate supply of whole blood is mandatory and complete replacement of the estimated blood loss is advisable. The importance of an immediately well-placed intravenous needle of adequate caliber cannot be overstressed. Too often this simple measure is delayed until shock and venipuncture by the laboratory technician have complicated its simplicity.

The object of a laparotomy is to control the bleeding. This can frequently be done by simple suture ligature. In the presence of the gravid uterus it is often impossible to identify the bleeding source and in such circumstances the uterus must be emptied, regardless of the gestational age of the fetus, to facilitate complete exploration of the pelvis. Hematomas must at times be evacuated by incising the overlying peritoneum. In extreme cases hysterectomy or ligation of the ovarian vein at its renal junction is necessary when the precise bleeding point cannot be identified.

Prognosis

The mortality rate reported by Hodgkinson and Christensen[1] in 1950 was 49.3 per cent. No maternal deaths have occurred in the 8 cases recorded since that time. The prognosis is generally much better in those cases of hemorrhage occurring during pregnancy than in those associated with labor. Seventy per cent of the former patients recovered versus 25 per cent of the latter. Confusion, indecision, and delay were responsible for many fatalities.

The prognosis for the fetus in utero de-

pends upon the gestational age and the degree of shock.

Summary

1. Two additional cases of hemorrhage from pelvic varicosities during pregnancy are presented.

2. A review of the literature reveals 81 previously presented cases with a mortality of 46 per cent. The mortality rate is higher in those cases associated with labor.

3. The good end results in the 2 reported cases can be attributed to early laparotomy and the absence of complicating labor.

4. The etiology, diagnosis, treatment, and prognosis of this obstetrical complication are discussed.

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Oxytocin in lactation

Clinical applications

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CLINICALLY, oxytocin has not yet won wide acceptance as an aid in puerperal lactation.[5, 14] This neglect seems odd in consideration of the well-documented[6, 8, 12, 13, 38] specific effect of oxytocin upon the contractile myoepithelium (basket cells of ectodermal origin[30] in intimate association with the mammary alveoli). It causes them to contract and thereby produces ejection of otherwise inaccessible milk into the larger lactiferous ducts where it becomes available to the suckling infant. In addition to this galactokinetic effect, much experimental work[3, 4, 33, 41] has been done to support the implication of an indirect galactopoietic action mediated through secretion of luteotrophic hormone (prolactin) by the adenohypophysis to augment and maintain milk secretion.

A growing body of clinical reports testifies to the awakening interest in this subject. The qualitative demonstrations of milk letdown in lactating women induced by parenteral administration of oxytocin[24, 27] have led the way to a series of experimental studies that attempted by various means to quantitate indirectly[23, 26] its potential beneficial action in emptying the alveoli and smaller ducts. Documentation of this effect was largely confined to cases in which puerperal engorgement or stasis problems were present.[2, 10, 11, 15, 17, 25, 36, 39] These published accounts presented groups of patients treated successfully with varying amounts of oxytocin preparations, administered by several available routes, including intravenous, intramuscular, and, more recently,[1, 18, 23, 40] intranasal. Several additional small series have appeared in which attempts at measurement of milk obtained under physiological conditions were made.[19, 35] In these latter, however, besides the lack of blind controls and randomization of material, the observations were carried out at some time after lactation had been fully in force, so that the possible influence which the drug may have had on the earlier lactation processes could not be indicated.

Breast pumping techniques to illustrate the oxytocin effect indirectly, while possibly satisfactory, may indeed have introduced unphysiological stimuli. Both hand and pump milking are known to alter milk yield,[22] and it follows, therefore, that data based on these techniques are not necessarily valid. The effect may be negative, causing temporary inhibition of the milk production (possibly on a neurogenic basis because of the unfamiliar or unacceptable manipulation required), or positive, augmenting production by the more complete emptying of the breast at each session. The use of infant weight increments before and after feeding, admittedly somewhat less accurate from the point of view of absolute precision, supersede the former artificial techniques as a more clear-cut index of milk made available to the infant under the influence of administered oxytocin. It is clearly understood that the child does not necessarily empty the breast at a given feeding.

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Method

The current study represents our attempt to determine critically by standard statistical techniques the clinical value of oxytocin in initiating, enhancing, and maintaining normal lactation, as measured by the amount of milk which the infant actually succeeds in obtaining at the breast.

Consecutive patients, all in-hospital puerperae, recently delivered at The Sloane Hospital for Women and desirous of breast-feeding their infants, were selected for study. Absolute consecutiveness was interrupted only for the deletion of the occasional mother with a major medical illness, or who had had a cesarean section, or who had been delivered of a sickly or premature infant or of twins.

The evaluation was conducted in a "double-blind," controlled manner with randomized assignment of precoded identical material, which had been prepared by Boissonnas[7] and preassayed for oxytocin activity. In addition to their corresponding placebos, material evaluated included intranasal spray preparations containing 40 I.U. per milliliter of synthetic oxytocin,* sublingual tablets containing 10 and 100 I.U., respectively, as well as 100 I.U. sublingual tablets with 1 Schering unit† of hyaluronidase added to aid local absorption.

Six distinct phases were involved in the conduct of these studies. First, a small blind pilot study, not detailed here, verified the probability of beneficial effect from oxytocin administered sublingually and intranasally in a liquid form. The second through fifth phases embodied the controlled studies outlined herein. These evaluated, respectively, (1) the intranasal preparation, (2) the 10 I.U. sublingual tablet, (3) the 100 I.U. tablet, and (4) the 100 I.U. sublingual tablet containing hyaluronidase. The sixth and final phase was concerned with comparative, objective demonstrations of the relative milk-ejection actions of the various substances tested. This was shown by the techniques, previously reported,[13] of direct measurement of milk-ejection pressures in unanesthetized women.

Treatment in all instances was begun at the first feeding of the first day following delivery, usually well within 24 hours after birth. It was continued for a total of 3 days, being administered prior to each nursing. The time limitation of 3 days was instituted in order to assure at least one day's observation of mother and baby after termination of the medication so as to note, where possible, potential ill effects from withdrawal prior to the patient's departure home, usually on or about the fourth postpartum day. Parenthetically, none were encountered.

Interruption of the treatment schedule was infrequently required for assorted reasons, but rarely for more than one or two feedings. Prompt reinstitution was almost always readily accomplished. Only one patient in the entire study had to be dropped because she electively refused to continue breast feeding once it had been initiated during the short period of treatment.

The hospital routine of infant feeding schedule was in no way altered to meet the particular needs of this study. Water by bottle was started 8 hours after delivery and repeated at 4 hour intervals. The infant was put to breast 12 hours after delivery and given water supplements on demand; breast feedings were continued at 4 hour intervals (except for the 2 A.M. feeding, at which time a standard bottle formula of evaporated milk, dextrose, and water was given). Feedings were limited in duration to 5 minutes at one breast only for the first 3 days (the duration of the treatment schedule), then increased to 10 minutes until the sixth day, 15 minutes until the ninth day, and so on. Breasts were alternated at each subsequent feeding. No manual expression or pumping was done. Ice compresses were applied for engorgement at will. No dietary restrictions were enforced.

The assigned treatment was applied just prior to each nursing period. The tablets

*Synthetic oxytocin supplied as Syntocinon, Sandoz Pharmaceuticals.

†One Schering A.G. unit of hyaluronidase is approximately equivalent[29] to 30 turbidity-reducing units, 90 viscosity-reducing units, 45 Benger units, and 30 U.S.P. units.

when used were allowed to dissolve sublingually beginning usually within 20 minutes before the feeding. The intranasal preparations were self-administered as a short firm spray (measured to be between 0.3 and 0.6 ml., or between 12 and 24 I.U.) just prior to placing the infant at the breast (usually about 5 minutes).

Evaluations were carried out by careful ante- and postcibum weighings of the infant at each nursing. The acknowledged inaccuracy of this coarse measurement, correct to the nearest 5 grams, prejudiced the study somewhat against the likelihood of our detecting significant effects, so that any encountered were felt probably to exist in fact. The errors inherent in the technique were, of course, present to the same degree in each of the groups studied due to the randomization of administration, so that no one subgroup was preferentially biased.

The differences in infant weight in grams before and after feeding was taken as the amount (by weight) of milk production available for that feeding. For all practical purposes, the gram weight of milk was essentially equivalent to its milliliter volume, since the specific gravity of mature breast milk varies from 1.028 to 1.035 and of colostrum, which contains more solid matter, from 1.040 to 1.080.[16] This contributes a unidirectional error of between 3 and 8 per cent to all such conversions. Similarly, the insensible weight loss of the infant during the interval of nursing, probably insignificant in amount, was not taken into account.

Compilation of material involved the determination of relative total daily production during the course of treatment, average production per feeding per day of therapy, and the over-all average available supply per feeding while under study. As an index of adequacy of lactation from the vantage of the infant's nutritional status, the loss of weight from original birth weight to that on the fourth day was noted. Subjective evaluation of discomfort during early critical days of lactation was also undertaken.

Table I. Intranasal spray data

	1st day	*2nd day*	*3rd day*
Total daily production (grams)			
Placebo	58.9	118.8	130.0
Oxytocin, 40 I.U. per milliliter	37.8	111.3	155.6
Average production per feeding (grams)			
Placebo	15.4	23.9	26.0
Oxytocin, 40 I.U. per milliliter	9.5	26.0	34.7

Material

Exclusive of the pilot studies, a total of 165 patients were evaluated. Ninety-nine of these made up the portion dealing with 10 I.U. sublingual oxytocin and its effect on lactation, comprising 33 who received the drug, 33 who were given placebo substitutes, and 33 untreated. Forty-eight were included in the evaluation of the 100 I.U. sublingual preparation, equally divided among those with added hyaluronidase and those without it, and among those given placebo and those given active drug. Eighteen patients constituted the intranasal group, half receiving placebo intranasal spray. This last group was originally made up of 20 patients, 2 of whom (one each from treatment and placebo groups) were lost to the study because of early technical problems with the spray devices. The only other patient lost to the study, one who had been given the 100 I.U. placebo containing hyaluronidase, has been mentioned above.

With reference to group make-up, all were relatively comparable (except for treatment modality, of course) with respect to age (average 26.2 years), parity (average 2.4, with 41.8 per cent primiparas), type of delivery (54.8 per cent spontaneous, 41.1 per cent low forceps), infant birth weight (mean 3,280 grams), complications of labor and delivery, and incidence and success rate of previous lactation attempts (64.7 per cent of the multiparas had made such attempts, and all but 10.9 per cent of these had ultimately succeeded). The absence of detectable differences in the composition of the several subgroups was felt to permit the statistical assumption that differences en-

Table II. Total daily production during treatment

	Number	1st day	2nd day	3rd day
Placebo	33	30.2 ± 5.5*	103.0 ± 10.2	160.8 ± 16.9
Oxytocin, 10 I.U.	33	55.3 ± 7.1†	135.5 ± 14.4	191.0 ± 20.2
No treatment	33	30.8 ± 6.6	98.0 ± 12.8	167.0 ± 15.9
Placebo	12	28.0 ± 6.3	77.1 ± 15.1	129.1 ± 12.3
Oxytocin, 100 I.U.	12	47.5 ± 12.9	117.5 ± 23.9	198.5 ± 57.0
Placebo-hyaluronidase	11	37.3 ± 10.7	118.2 ± 23.0	183.6 ± 24.3
Oxytocin, 100 I.U., hyaluronidase	12	53.4 ± 5.4	121.3 ± 10.1	193.2 ± 44.1
All placebos	56	31.2 ± 5.2	100.4 ± 12.0	159.0 ± 22.0
All treated	57	53.4 ± 5.4†	121.3 ± 10.1	193.2 ± 44.1

*Standard error is indicated by ±; the unit of measurement is grams throughout.
†$p = 0.01$.

countered between them could probably be attributed to the single controllable variable, namely the mode of therapy applied. This consideration is important in light of the demonstrated diminution in milk production with advancing age and progressive parity.[22, 37]

Data were gathered with reference to gram weight (infant weight increment) of milk ingested at each feeding, as distinguished from the total yield of the patient. The unnatural stimuli of manual or mechanical expression used to determine residual milk were avoided so as not to influence current or subsequent production in any way. Thus the total yield was not measured, and it was not considered essential, in that the moiety not obtained by the infant during a given feeding was not actually available to him within the scope of his ability to extract it from the larger lactiferous ducts by suckling. This view was firmly adhered to despite the contention[20] that the last portion of human milk obtained by pumping is richer in fat percentage content than the first part. Apropos of this matter of the nutritive value of the "colostrum phase" of milk production (the termination of which is variously placed at 3 to 20 days[22]), it is documented[24] that there are 57 utilizable kilocalories* per 100 ml. of human colostrum (first to fifth day of lactation). This is only 12.3 per cent less than that of so-called mature milk, which contains 65 kilocalories per cent (beyond the tenth day of lactation). This indicates that colostrum is, therefore, apparently quite satisfactory from the nutritional viewpoint. In addition, the strikingly high percentage of globulin fraction[9] present in colostrum has been considered an attribute in providing the newborn with protective antibodies. This is perhaps not too important in light of the observations that the placental transfer of this substance is high.[20]

*Kilocalories, calculated on the basis of 8.8 calories per gram of fat, 3.9 calories per gram of carbohydrate, and 4.3 calories per gram of protein.

Results

The intranasal route of administration was briefly investigated and was found to be disappointing in its clinical action (Table I). It was later determined (vide infra) that the material is quickly absorbed by the nasal mucosa and is promptly and strongly effective. That this was not reflected in productivity might have been a function of its short duration of action. Indeed, the effect noted was one of apparent diminution in milk production. It is possible that transitory inhibition of milk ejection, previously demonstrated[13] to follow massive myoepithelial responses, may have resulted in this unexpected finding. Similarly, in dairy animals,[21] undue delay, even quite briefly, between the stimulus for "letdown" (milk ejection) and the actual milking has been shown to be associated with inhibitory effect on both ejection and production. This was felt to be due to the rapid dissipation of circulating oxytocin. It is conceivable that, whereas the sub-

Table III. Average production per feeding

	Number	*1st day*	*2nd day*	*3rd day*
Placebo	33	8.8 ± 1.5	22.5 ± 3.0	33.7 ± 3.3
Oxytocin, 10 I.U.	33	13.9 ± 1.4*	28.9 ± 3.2	39.6 ± 4.1
No treatment	33	8.1 ± 1.8	19.8 ± 2.5	33.9 ± 3.2
Placebo	12	7.5 ± 1.6	17.3 ± 2.9	23.6 ± 6.2
Oxytocin, 100 I.U.	12	12.3 ± 3.3	24.4 ± 4.6	39.8 ± 10.8
Placebo-hyaluronidase	11	10.7 ± 2.7	24.7 ± 4.7	38.2 ± 5.0
Oxytocin, 100 I.U., hyaluronidase	12	14.5 ± 3.5	20.3 ± 2.4	42.5 ± 5.4
All placebos	56	8.9 ± 1.4	21.8 ± 2.0	32.5 ± 2.5
All treated	57	13.7 ± 1.4*	26.1 ± 2.1	40.3 ± 3.3

*p = 0.01.

lingual tablets gave prolonged, low dosage stimulation, the intranasal sprays gave only short acting, quickly dispelled actuation.

The total obtainable daily supply (Table II), which as previously noted need not have reflected the actual total milk production in the breast, was demonstrated to be uniformly greater in patients receiving sublingual oxytocin than in those untreated. This was seen throughout the course of these studies regardless of the amount of drug given. The average total obtained on the first day of treatment in the 57 patients who received the drug sublingually in any dose (53.4 ± 5.4 grams) was significantly greater (p = 0.01) than that of the 56 corresponding placebo-treated patients (31.2 ± 1.9 grams). The differences for the second and third days of treatment, while showing the same trend toward higher milk production, could not be shown to be statistically significant.

Comparisons between the 10 and the 100 unit dosage trials yielded no differences worthy of note, the data indicating essentially identical effects. Based on the demonstration of a sigmoid curve of log dose-response of milk-ejection pressure with peak action for oxytocin at a dosage level of about 15 mU. intravenously (beyond which no further augmentation of effect was attainable), this similarity of effect of the 10 unit dose and its tenfold counterpart was to be anticipated. Inhibition of effect by larger doses, shown by intravenous administration of upwards of 3,000 mU. of oxytocin[2] was not seen here. The amount absorbed sublingually in the current series, however, was possibly not of this order. This unrealized inhibition may have had a basis similar to that noted with respect to the intranasal route.

An attempt to evaluate the well-documented emotional influence[24] on milk supply was done by contrasting a placebo-treated group with a comparable unselected group (assigned by alternation) who were given no treatment. No detectable differences (Table II) were encountered, denying the presence of a placebo effect, an important consideration, and also indicating the statistical reliability of the techniques used. Neurogenic factors, as potential positive or negative influences, appeared to have been negated by the leveling effect of the approach used in this study, the effects of factors other than that of treatment tending to be eliminated.

The average amount of milk obtained per feeding (Table III) during treatment with sublingual oxytocin paralleled almost precisely that for total daily yield, with significantly increased first day production recorded for all treated patients (13.7 ± 1.4 Gm. per feeding) as compared with that of the grouped placebo-treated patients (8.9 ± 1.4 Gm.). Similar trends on subsequent days were also seen. Patients treated with 10 I.U. oxytocin tablets produced 13.9 ± 1.4 Gm. per feeding on the first day, as contrasted to 8.8 ± 1.5 Gm. for corresponding patients treated with placebos, a statistically valid difference (p. = 0.01).

Variations in volume of production, carefully studied with pumping techniques,[31] have demonstrated that the maximum rate

of increase in secretion is on the third day of nursing. A definite leveling off of secretory rate occurs from the fourth day on, but the actual peak of productivity may not be reached until some time later. The data presented here for yield per feeding as well as that for total daily output closely parallel these curves. The production of milk, however, appears to increase most rapidly on the second day. There is a twofold increase (227 per cent) in total production from the first to the second day (threefold, or 322 per cent, in the placebo group), while only a 159 per cent change from the second to the third day (same as in the placebo group). It is possible that the mechanical expression methods may have impeded the earlier rapid progress which may be expected to take place as seen in these studies. The potential temporary inhibition, perhaps as a result of emotional revulsion with regard to the pump, has previously been authenticated.[22] The apparently slower relative daily rise in the oxytocin-treated group, despite the fact that the absolute values were consistently higher throughout, is a reflection only of the significantly greater initial surge of production attributable to the treatment.

With regard to the over-all average production per feeding as related to treatment (Table IV), the aforementioned differences are more or less eradicated. The leveling effects of the increased productivity of the second and especially the third day detract from the value of the data, particularly in view of the fact that the yield curves for placebo- and drug-treated patients appear to approach each other with each advancing day. It is suggested by the latter phenomenon that extrapolation of these curves will result in ultimate identical levels of milk production; and further that oxytocin, therefore, does not seem to influence, even indirectly as has been suggested,[3, 4, 33, 41] milk secretion per se. The advantage of using oxytocin is not in its dubious power to stimulate alveolar milk production, but rather in its documented ability to make the secreted milk available to the infant by myoepithelial activation.

With reference to infant loss of weight from birth to the end of therapy, the data were as follows: babies of placebo-treated mothers lost on the average 89.2 grams, while those of corresponding 10 I.U. oxytocin-treated mothers lost only 67.9 grams; placebo 122.7 grams, corresponding 100 I.U. 89.1 grams; placebo with hyaluronidase 90.0 grams, corresponding 100 I.U. with hyaluronidase 112.7 grams. Except for the hyaluronidase groups, a trend toward less weight loss in infants whose mothers were treated with oxytocin is exhibited. The marked variations encountered in this aspect of the study minimizes the statistical value of these data, but the tendency noted appears to reflect increased initial milk yields. Indeed the differences found are of the same order as the differences in milk production.

Subjective discomfort, an important clinical consideration in the early phases of lac-

Table IV. Over-all average production per feeding

	No.	*Mean*
Placebo	33	24.3 ± 2.1
Oxytocin, 10 I.U.	33	29.8 ± 2.6
No treatment	33	23.1 ± 2.1
Placebo	12	22.5 ± 3.3
Oxytocin, 100 I.U.	12	28.4 ± 5.2
Placebo-hyaluronidase	11	26.3 ± 4.2
Oxytocin, 100 I.U., hyaluronidase	12	28.7 ± 3.4

Table V. Pain during lactation

	Total	*No. with pain*	*Per cent with pain*
Placebo	33	13	39.4
Oxytocin, 10 I.U.	33	9	27.3
Placebo intranasal	9	4	44.4
Oxytocin, 40 I.U. per milliliter	9	2	22.2
Placebo	12	6	50.0
Oxytocin, 100 I.U.	12	3	25.0
Placebo-hyaluronidase	11	6	54.5
Oxytocin, 100 I.U., hyaluronidase	12	4	33.3
All placebos	65	29	44.6
All treated	66	18*	27.3*

*p = 0.03.

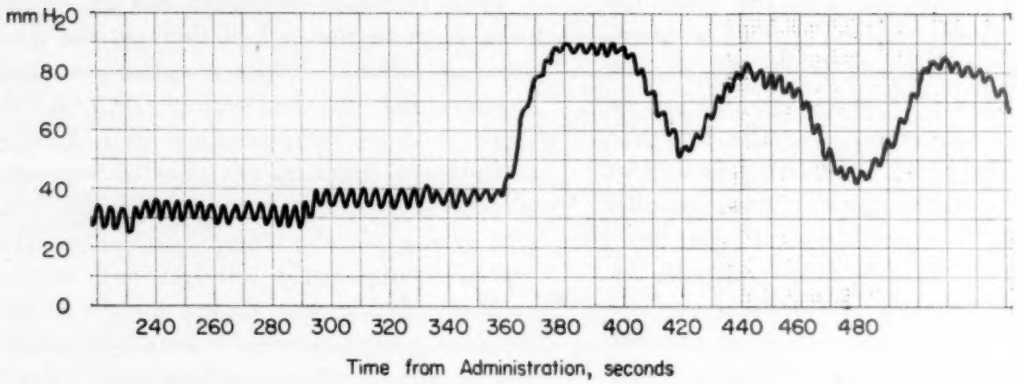

Fig. 1. Milk-ejection pressure recording in a primipara on the second day of lactation. Millimeters of water pressure versus time in seconds after the sublingual administration of a tablet containing 10 I. U. of synthetic oxytocin. The initial ejection wave begins after 6 minutes, rises 50 mm., lasts about 65 seconds. Subsequent waves follow in irregular succession for as long as 40 minutes; peaks of amplitude vary between 30 and 50 mm. H_2O.

tation processes, was evaluated because of the strong impression, verified in several previous uncontrolled studies,[1, 11, 18, 25] of beneficial effect. No attempt was made to distinguish (it is doubted if such distinction is at all possible) between pain due to congestive engorgement and that due to milk stasis engorgement. With all treated patients grouped together (Table V), significant differences were found between oxytocin-treated (27.3 per cent experienced pain) and placebo-treated (44.6 per cent pain) groups. Similar differences were equally reflected in the several treatment subgroups without variation. The relief of pain in early lactation appeared to result from the use of oxytocin. The mechanism by which this action was mediated was unknown. There were no consistent objectively demonstrable findings which mirrored the alleviation of pain, clinically apparent engorgement being found with and without pain, and pain being present with and (rarely) without engorgement.

Objective demonstrations of the effect of the several preparations were carried out in order to attempt to define their relative potency, as well as the time of onset and the duration of action. The method used, previously detailed,[13] measured milk-ejection pressure changes directly in the unanesthetized patient. No effect was obtained from any of the placebo preparations, including the sublingual and intranasal varieties, and those with added hyaluronidase. The milk-ejection pressure changes recorded following the administration of 10 I.U. oxytocin tablet sublingually (Fig. 1) were very slow in onset, of low magnitude, and irregular, but were quite prolonged. Onset of effect took place usually after about 6 minutes (2 to 10 minutes). Intraductile pressure peaks occurred in the range of 30 to 50 mm. of water. Waves recurred irregularly at 60 to 80 second intervals. The duration of action was of the order of 30 minutes (20 to 40 minutes), continuing for as long as the tablet continued to dissolve under the tongue. Recordings after the 100 I.U. tablet, as well as after the 100 I.U. tablet containing hyaluronidase, were essentially identical in all details, indicating either that the absorption rate did not change, or more likely that the effect seen following the 10 I.U. tablet was a maximal physiological response.

The intranasal spray containing 40 I.U. per milliliter (Fig. 2) produced very rapid, high intensity, short-lived milk-ejection responses. Major reactions were seen in about 2 minutes (1.5 to 3 minutes), reached extremely high peaks of pressure (beyond the 80 mm. of water range of our recording equipment), and lasted a variable length of time, usually not exceeding 2 minutes. Following this intense reaction, no further activity could be elicited by any means, in

many cases, for as long as half an hour (10 to 30 minutes), indicating the existence of the inhibitory effect to which we have previously alluded, and perhaps accounting for our inability to demonstrate effectiveness of this modality of administration clinically.

Comment

It has been demonstrated quite clearly, with satisfactory statistical verification, that initiation of the clinical process of milk production from the infant's viewpoint (not necessarily with reference to lactogenesis) is enhanced significantly by oxytocin administration in a sublingual tablet form. This appears to be mediated through the contraction of the myoepithelial elements surrounding the alveoli and smaller ducts. This in turn brings about the transport of previously secreted milk into the larger ducts where it becomes available to the suckling infant.

Milk, in significantly larger initial quantities and at an earlier time, is obtained by the newborn when the synthetic oxytocin preparation is administered to his mother prior to each feeding (as compared with infants whose mothers were given placebo forms or no treatment at all). The ultimate amount per feeding or level of total daily yield does not seem to be any greater than that induced by the normal unstimulated functionings of the hypothalamic-hypophyseal system and associated mechanisms, given sufficient time to evolve. The initial surge of nutritive colostrum made available to the infant, however, is perhaps an important component of successful lactation. Data on end results with regard to success in this series, however, are meaningless because there are so many other factors bearing on it.

The efficacy of the sublingual preparation appears to be due to its prolonged action and relatively low intensity. The latter has been measured to be the equivalent of repeated intravenous doses of about 10 to 15 mU. of oxytocin.[18] The anticipated greater activity of 100 unit tablets, which were expected to add higher intensity to long action, was not realized. It is reasoned that maximal effects (as seen in the sigmoid log dose-response curve) had been reached at the lower dosage level. The inhibitory effect of massive doses, as demonstrated by the administration of the rapidly absorbed spray of high concentration oxytocin solution, was apparently not attained by the 100 I.U. tablet. It seems that the latter quantity fell fortuitously above the level of maximal effect but below that necessary for inhibition. The alleged additional absorption due to hyaluronidase did not appear to raise the level into the inhibitory range either. It is suggested that the absorptive action of hyaluronidase may have been inhibited by salicylates which puerperae are frequently given for various discomforts; such relevant inhibitory effects of salicylates have been well documented.[32]

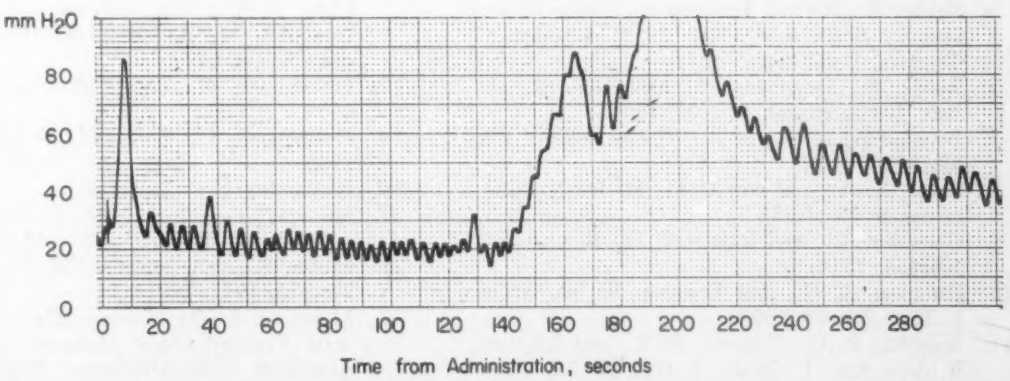

Fig. 2. Identical set-up as in Fig. 1 in same patient 1 hour later. At onset of record is seen a sharp initial peak representing strong inhalation at time of spray administration of 0.5 ml. solution containing 20 I.U. of synthetic oxytocin, intranasally. Effect begins 2 minutes and 18 seconds later and rises above 80 mm. H_2O. A prolonged refractory period follows.

Summary and conclusions

A double-blind, controlled, randomized series of studies has been conducted to determine the effect of synthetic oxytocin, in intranasal spray and sublingual tablet forms, on initiation, enhancement, and maintenance of the early phases of lactation.

The clinical parameters studied included average yield obtained per feeding, total daily production, over-all average production during treatment, infant weight loss, and the subjective appreciation of pain during early lactation. Objective observations were also made to define relative milk-ejection potency, time of onset, and duration of action.

It was found that oxytocin, administered as a 10 I.U. sublingual tablet prior to feedings, aided in the prompt initiation of lactation, as demonstrated by significantly greater amounts of milk obtained by the newborn.

This effect was not increased by a tenfold increase in dosage, nor by the addition of hyaluronidase to aid sublingual absorption.

Ultimate total yield of milk did not appear to be augmented by the use of oxytocin, levels of production with and without treatment tending to approach each other with the passage of time.

Intranasal administration of solutions containing 40 I.U. per milliliter of oxytocin appeared to have an inhibitory effect on milk yield; the theoretical considerations have been discussed.

Definite subjective relief of breast pain in early lactation, by a mechanism as yet unknown, was evidenced during treatment with oxytocin.

Milk-ejection pressure studies have been presented to illustrate that adequate sublingual absorption of oxytocin takes place and produces prolonged activity of low magnitude. Intranasal absorption was seen to induce rapid, high intensity, short-lived intraductile pressure changes.

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Influence of hormone dosage and time of administration on suppression of lactation

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THE superiority of androgen-estrogen combinations for suppression of lactation in the immediate postpartum period is well substantiated by clinical findings.[1-7] While either androgen or estrogen alone is adequate preventive treatment, when given together in balanced proportions, they largely cancel out unwanted actions in sexual spheres encountered with predominance of one or the other hormone. The hirsutism, voice changes, and delay in uterine involution and onset of normal menses characteristic of androgen therapy and the secondary breast engorgement, uterine bleeding, and slow rate of uterine involution associated with high estrogen titers in the puerperium are essentially eliminated by the use of hormone combinations.[1, 3, 6, 8] The development of long acting esters of the naturally occurring sex steroids has further simplified management of what is a normal physiologic event following childbirth, but an undesirable one for increasing numbers of women who choose not to nurse their newborn infants.[8, 9]

While hormone suppression of postpartum lactation is certainly more satisfactory in terms of patient comfort than the use of tight breast binders, ice bags, or fluid intake restriction, difficulties have been encountered in achieving complete inhibition of pain, breast engorgement, and lactation in all treated patients. With oral hormone preparations, there is always the likelihood of incomplete dosage particularly when the patient returns home and plunges into the unusual and time-consuming program required for care of the infant. From recent reported experiences, however, there appears to be a physiologic explanation for inconsistencies in results obtained in various studies. Time of administration has been found to be equally important in influencing the therapeutic outcome as adequacy of dosage. Institution of therapy during active labor,[6, 7] or immediately following delivery[7, 8, 10] accomplishes the desired control of lactation and associated breast manifestations in a very high percentage of nonnursing mothers without affecting the subsequent course of labor or postpartum physiologic readjustments. An exogenous supply of hormones given during parturition continues the inhibition of anterior pituitary production and release of the lactogenic hormone, prolactin, maintained throughout pregnancy by high levels of endogenously produced ovarian hormones. It is the sharp fall in circulating ovarian hormones following expulsion of the placenta that essentially initiates lactogenesis and, consequently, suppressive doses of hormones are most efficiently administered before emptying of the uterus triggers the chain of events culminating in formation of milk. While lactation is by no means a simple phenomenon, on the basis of known physiologic interrelationships, a rational approach to suppression is feasible.

Since the obstetric patient cannot tolerate oral medication for several hours after delivery, the urgency of prompt hormone treatment compels use of a parenteral preparation. When sex steroids with a prolonged action are employed, they dispose of the daily injections or daily pills while the pa-

tient is confined to the hospital as well as the dependency of successful therapy upon continuation of medication following discharge. The experience reported here involves a balanced combination of testosterone enanthate and estradiol valerate dissolved in sesame oil (Deladumone). Each milliliter of low viscosity solution provides 90 mg. of the testosterone ester and 4 mg. of the estrogen. Absorption is believed to be continuous beginning shortly after injection and extending for a period of 10 to 14 days. In other investigations with fair sized clinical groups, a single injection of this preparation given on the delivery table successfully prevented breast engorgement, leakage, and pain during physiologic adjustments to the avoidance of breast feeding.[6-10] Dosage ranged from 1 to 4 ml. and was administered as early as the end of the first stage of labor or immediately after delivery. A greater percentage of excellent results was obtained when treatment was delayed no longer than 4 minutes after ejection of the placenta.[8] In the present study, 2 separate courses of therapy were employed in 2 relatively small groups of patients. Benefits with Deladumone were explored at 2 dosage levels, one injected 1½ to 2 hours after delivery and the other during the second stage of labor.

Procedure

An initial series of 25 patients encountered in a private obstetrical practice, who desired to avoid nursing their newborn infants, received a single intramuscular injection of 2 ml. of Deladumone as soon as it was practicable after they had been delivered. As time permitted, treatment was given from 1½ to 2 hours following expulsion of the placenta. Of this group, 22 women reported previous pregnancies and other practices for suppression of lactation. Once the injection was administered, no special breast care was prescribed. Patients were requested to wear ordinary brassieres, but tight binders, ice bags, and restriction of fluid intake were strictly forbidden. Subjective complaints of engorgement and pain and the amount of treatment necessary to relieve symptoms were the primary factors considered in the appraisal of the efficacy of the hormone preparation and the suitability of dosage and time of administration. Five categories of subjective manifestations were established: none, minimal, moderate, aspirin-acetophenetidin-caffeine compound required for control, and codeine required for control. Observations were also made of the time of onset and duration of breast symptoms where they occurred. Daily contact was maintained with all patients during the 5 days of hospitalization and findings were recorded on the eighth, tenth, and fourteenth postpartum days.

A second series of 50 patients received 4 ml. of Deladumone as 2 equal doses injected into either gluteal muscle during the second stage of labor. This course of therapy was undertaken when the earlier program failed to achieve the desired suppressive effect in a sufficient number of patients. Because the insufficiency could not be attributed to any one factor, the dosage was increased and the time of administration set forward. In this group, Deladumone was injected an average of 34.6 minutes prior to delivery. As before, no special breast care was carried out. For purposes of comparison, the same criteria were employed for appraisal of treatment, and follow-up was identical for both clinical groups.

Results

For control of postpartum lactation and associated breast manifestations in the nonnursing mother, a single injection of 4 ml. of Deladumone given during the second stage of labor proved a remarkably effective regimen and far superior to the postdelivery administration of a 2 ml. dose in consistency and completeness of suppressive action. Within the limitations of a relatively small clinical group and two fixed procedures, the hormone preparation appeared to produce a high percentage of excellent results when employed in adequate dosage and injected prior to delivery. Findings were considerably less favorable with the lower dosage postdelivery schedule (Tables I and II).

Of the 25 patients given a single injection

Table I. Onset and duration of postpartum breast manifestations

Course of therapy	Postpartum day									
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*10*	*14*
2 ml. 1½ to 2 hours after delivery (total, 25 patients)	0	0	7	15	14	no contact		9	4	1
4 ml. during second stage of labor (total, 50 patients)	0	0	0	1	0	0	1	0	3	0

of 2 ml. of Deladumone within 1½ to 2 hours of delivery, 21 complained to some degree of engorgement and pain while only 4 were completely asymptomatic. The onset and duration of symptoms may be seen in Table I. All days on which complaints were expressed have been counted. In our experience with untreated patients, breast symptoms are most apparent on the third postpartum day. From Table I, it appears that a delay of 24 to 48 hours in onset of symptoms occurred in some cases in this series. Discomfort was minimal in 12 and moderate in 7 patients, thus requiring no special treatment. On the other hand, 2 women required codeine for control of pain (Table II). There were 12 cases where breast engorgement continued following discharge from the hospital. All were minimal in nature except for one which was judged moderate. Three patients experienced secondary engorgement while at home. While these results are not particularly impressive, 7 patients given medication for suppression of lactation during previous pregnancies volunteered the information that discomfort was less with Deladumone.

Table II. Comparative effectiveness of two different courses of therapy

Degree of discomfort	No. of patients	
	2 ml. 1½ to 2 hours after delivery	*4 ml. during second stage of labor*
None	4	45
Minimal	12	5
Moderate	7	0
Aspirin-acetophenetidin-caffeine compound required for control	0	0
Codeine required for control	2	0
Total No. of patients treated	25	50
No. of patients with symptoms	21	5

In contrast to observations in the initial series, however, only 5 of the 50 patients given 4 ml. of Deladumone during the second stage of labor complained of breast discomfort in the puerperium (Table II). Pain and engorgement were minimal in these cases and required no special care or analgesic medication for control purposes. Generally, patients expressed extreme satisfaction with the outcome of the treatment and, since subjective factors are of considerable importance in the determination of what constitutes minimal, moderate, or severe pain or discomfort, this may be considered an authoritative statement of the efficacy of hormone action. As before, when symptoms occurred, a delay in onset was observed (Table I). No difference in response was noted between primiparous and multiparous patients.

No serious reactions of any kind occurred during this investigation. Administration of Deladumone during labor in no way affected progression to delivery. In the first group of 25 patients, there was one apparent allergic reaction of a minor nature manifested by an itching wheal at the site of injection. This subsided spontaneously without treatment. There were no allergic reactions in the second group although several patients showed erythematous indurated areas at the site of injection, probably as a result of the technique of injection when labor was progressing rapidly. The single injection was not found to alter the character of the lochia. It was our impression, however, that uterine involution did not proceed as rapidly in treated as in untreated patients. Accordingly, in patients of the first group, the height of the fundus from the symphysis was measured

on the day of discharge. The average for the women treated with Deladumone was 10.7 cm. compared with 11.3 cm. for patients receiving stilbestrol. In contrast, nursing mothers measured 6.7 cm. No bleeding or masculinization was observed.

Comment

Although lactogenesis is by no means a simple phenomenon, sufficient evidence is available to establish firmly the interrelationship between the sex steroids and prolactin produced and released by the anterior pituitary gland. During pregnancy, the presence of ovarian hormones in high titer is believed a primary barrier to milk formation, exerting a direct as well as a secondary influence on physiologic mechanisms. The twofold persuasion comprises inhibition of the production and release, or both, of the pituitary hormone and also the conditioning of breast tissue so that it is refractory to prolactin stimulation. On the other hand, the abrupt fall in ovarian hormone levels occurring at parturition frees the pituitary from inhibitions maintained in the antenatal period, accelerating the formation of prolactin and initiating active lactation. In the nonnursing mother, pituitary suppression may be continued in the puerperium by means of an exogenous supply of androgens, estrogens or, preferably, a combination of both. Evidence available supports at least 3 fundamental physiologic requisites for satisfactory control of lactation: (1) suppressive hormones should be administered prior to delivery; (2) these should be given in adequate amounts; (3) they should possess the prolonged action to maintain inhibition throughout postpartum adjustment to the avoidance of breast feeding.

Summary and conclusion

The most satisfactory method of lactation suppression in our experience employed a parenteral preparation containing the long-acting esters, testosterone enanthate and estradiol valerate (Deladumone). A single injection of 4 ml. given intramuscularly during the second stage of labor proved highly effective for control of engorgement and pain, and superior to 2 ml. given as soon as feasible after the child has been delivered, for maintenance of breast comfort in the puerperium. No attempt was made during this investigation to determine the efficacy of 4 ml. doses given post partum. Aside from the obvious advantages of elimination of the daily oral dosage for varying periods or frequent injections, the use of Deladumone was strikingly free from the secondary engorgement frequently seen with stilbestrol following discharge from the hospital. Where symptoms of engorgement occurred, medication may have contributed to a delay in onset in some cases beyond the third or fourth day on which they are usually observed. Only 10 per cent of patients treated with 4 ml. of Deladumone during labor experienced symptoms of postpartum breast engorgement and none required special treatment for their discomfort. The administration of the hormone combination during labor in no way affected the subsequent course to termination.

It is concluded that a parenteral preparation of long-acting androgen and estrogen provides early, adequate, and sustained suppressive activity requisite for breast comfort in the nonnursing mother.

The Deladumone employed in this study was supplied through the courtesy of Dr. E. C. Reifenstein, Jr., The Squibb Institute for Medical Research, New Brunswick, New Jersey.

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Use of a sulfonamide vaginal cream post partum

A controlled "blind" study of 700 patients

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VAGINAL creams containing sulfonamides have been recommended for routine use in the postpartum patient.[1, 2] Indeed, it has been reported that in patients using a sulfonamide vaginal cream post partum, "the incidence of postpartum endocervicitis was practically nil, and to date we have not had to treat a cervix at the sixth week post partum."[1] Furthermore, it has been stated that patients using such a preparation post partum had a much lower incidence of morbidity and breakdown of suture lines of episiotomies than did control cases.[1] If these advantages said to accrue from the use of sulfonamide creams post partum should really exist, without any apparent disadvantages, the routine use of such preparations in postpartum patients might well be worth while. However, the manner in which the treated and untreated patients were selected and evaluated in these reports is unclear and leaves open the possibility of unconscious bias in the observations. Accordingly, a study was carried out in which the patients using a sulfonamide cream vaginally post partum were completely randomized with a control group, and in which the observers were unaware of whether the patients had used the creams or not.

Methods and materials

Seven hundred consecutive ward obstetrical patients who were delivered vaginally served as subjects. All patients delivering on certain days of the week were given an unidentified tube containing a triple sulfonamide cream* and a container of disposable vaginal applicators (each applicator delivered approximately 5 ml.). Beginning on the first postpartum day and continuing for the entire hospital stay, each patient was individually supervised daily by the same nurse in the instillation of the cream intravaginally. (Postpartum days in the hospital were 4 to 8, average 5.) Each patient was instructed to continue the daily instillation of the jelly after going home, until all disposable applicators had been used. All patients delivering on alternate days of the week were untreated and served as controls.

Since any cream placed in the vagina might conceivably have some effect, and, indeed, would have to contain preservative agents to reduce bacterial and fungus growth while the cream was stored in its tube, no cream could serve as a true placebo. Hence, the control subjects received no vaginal instillation of any kind. Three hundred patients who used the cream once daily for 7 days were available for comparison with a like number of patients in the untreated control group. A second treatment group consisted of 100 patients who used the cream once daily for 14 days. Patients delivered by cesarean section were the only ones excluded from the study. The patients' 6 weeks postpartum examinations were performed by the physicians working in the

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*Triple Sulfa Cream, supplied by the Ortho Pharmaceutical Corporation.

Outpatient Section. None knew which patients had used the cream. Each patient's record included a simple form containing questions concerning leukorrhea and vulvar and vaginal itching and burning as well as diagrams of various size cervical erosions. The examiners merely checked the appropriate answers and diagrams. The results were then tabulated and analyzed statistically.

Results

The 300 patients who used the triple sulfonamide cream intravaginally for 7 days exhibited no statistical differences (chi square analysis) from the untreated control group with respect to parity, incidence of spontaneous and forceps deliveries, or incidence of episiotomies (Table I). There also was no significant difference (chi square analysis) between the treated and untreated (control) groups in the appearance of the cervix 6 weeks post partum, as classified by the examiners (Table I). The cervix was judged to be healthy in 60 per cent of the treated and in 63 per cent of the untreated patients. The cervix was slightly eroded in 27 per cent of the treated group and 22 per cent of the control patients. The cervix was considered to be moderately eroded in 10 per cent of the treated patients and much eroded in 3 per cent, compared with 11 per cent and 4 per cent in the untreated group. These differences are not statistically significant. There were also no significant differences in the incidence of leukorrhea and vaginal burning or itching between the treated and untreated groups (Table I).

There also was no significant difference in the incidence of hospital morbidity between the two groups (morbidity as defined by the Joint Committee on Maternal Welfare, United States,[8] i.e., temperature of 100.4° F. taken by mouth four times daily, on any two of the first 10 postpartum days, exclusive of the first 24 hours). The incidence of morbidity in the treated group was 3.7 per cent, compared with 7.7 per cent in the control group (Table I). The likelihood of such a difference in morbidity rate being due to chance alone is less than 10 in 100, but greater than 5 in 100 and, hence, not statistically significant (chi square = 3.772, $P > 0.05 < 0.10$).

When it became apparent that the patients treated for one week with the sulfonamide cream exhibited no significant differences from those who were untreated, the length of treatment was extended to 2 weeks with the thought that more prolonged therapy might prove beneficial. One hundred consecutive postpartum patients used the sulfonamide cream intravaginally under daily direct supervision during hospitalization and thereafter while unsupervised at home, for a total of 14 days. In this group, too, there were no significant differences from the control group (Table I) as regards parity, the incidence of spontaneous or for-

Table I. Triple sulfonamide cream

	Used intravaginally once daily		
	For 1 week (300 patients) (%)	*For 2 weeks (100 patients) (%)*	*Control (300 patients) (%)*
Postpartum parity			
1	30	38	38
2	32	25	29
3	21	22	16
4	9	8	8
5 or more	8	7	9
Delivery			
Spontaneous	72	66	71
Forceps	28	34	29
Episiotomy	59	69	66
Cervix (6 weeks post partum)			
Healthy	60	72	63
Eroded			
Slight	27	17	22
Moderate	10	9	11
Much	3	2	4
Local symptoms			
None	49	61	65
Itching	5	3	4
Burning	2	1	2
Leukorrhea			
None	55	61	58
Moderate	42	37	40
Much	3	2	2
Patients morbid	3.7	1.0	7.7

ceps deliveries, and episiotomies. At 6 week follow-up examination there were also no significant differences in the incidence or extent of cervical erosions or the incidence of leukorrhea, vaginal burning, or pruritus. The incidence of hospital morbidity was 1 per cent in the treated group, compared with 7.7 per cent previously found in the untreated group. This difference we consider of modest statistical significance, that is, the likelihood of a difference of this magnitude occurring due to chance alone is greater than 2 in 100 but less than 5 in 100 (chi square = 4.72, $P > 0.02 < 0.05$). When the two treatment groups are pooled, giving a total of 400 cases to compare with the 300 untreated controls, the over-all incidence of morbidity in the treated group is 3 per cent. This is a highly significant difference from the 7.7 per cent incidence in the untreated group. The likelihood of such a difference occurring from chance alone is less than 1 in 100 (chi square = 6.81, $P < 0.01$).

Side effects

One patient developed intense vaginal pruritus 24 hours after starting sulfonamide instillations. She had no history of allergies or previous exposure to sulfonamides. Examination showed no visible abnormalities, but vaginal applications were discontinued and the patient removed from the study. The itching disappeared in 24 hours.

Comment

It seems important to point out that the intravaginal instillation of this sulfonamide cream in postpartum patients can produce demonstrable and significant sulfonamide levels in the blood.[2] Indeed, we have previously found that 200,000 units of penicillin placed in the vagina resulted in quicker and higher blood levels and greater urinary recovery of penicillin than when the same subjects were given the identical dose by mouth.[4] The lower morbidity rate among the treated patients in the present study might be related to systemic effects of the sulfonamides as well as to a reduced vaginal bacterial flora.

The appearance of only one presumed instance of sensitivity to the sulfonamides was surprising. It is possible that the elevated blood levels of adrenal cortical hormones of late pregnancy may help protect against sensitivity reactions.[5]

Summary

Six hundred postpartum women who had been delivered vaginally were randomly divided into two groups, one of which received a daily vaginal instillation of a sulfonamide cream for 7 days post partum. The patients' conditions were evaluated at 6 weeks follow-up examination by physicians who were unaware which patients had used the vaginal cream. There were no significant differences in the treated and untreated groups in the incidence of cervical erosions, leukorrhea, or vaginal burning or pruritus. An additional 100 patients used the cream for 14 days. This group also showed no differences from the control subjects with respect to the above factors. Comparison of the 400 treated patients with the 300 control patients revealed a lower incidence of hospital morbidity in the treated group. One instance of presumed sensitivity to the vaginal cream was observed.

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Subjective evaluation of an enzyme preparation in episiotomy pain

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ONE of the most frequent postpartum complaints is episiotomy pain. We assume the episiotomy pain is due to the swelling of the tissue, hemorrhagic contusion of the perineal muscles, and the issue trauma associated with delivery. Enzyme preparations have been utilized for the resolution of inflammation and edema.[1-4] We have reviewed several articles pertaining to this. None have indicated whether or not these drugs would be of value in episiotomy pain. We felt that such a drug might be of value for this purpose. Therefore, the following work was instituted.

This paper represents a double-blind study using such a preparation (Orenzyme)* to evaluate its worth for this purpose.

Procedure

All patients (without exception) who had an episiotomy were placed alternately on the drug or the placebo as soon as practicable after their arrival on the postpartum floor. The patients received 2 tablets four times a day. This regimen was continued until the patient's discharge, which averaged 4 to 5 days after delivery.

The patient was not informed as to the specific nature or purpose of the drug. None of the personnel associated with the study knew which tablet contained the drug. Each patient was given a form on which were written 7 symptoms (nausea, vomiting, afterpains, bleeding, stitch pain, breast discomfort, and hemorrhoidal pain) and was told to grade the severity of these from 1 to 4.

Results

A total of 500 patients comprised the study. Sixty-seven patients were deleted from the study because they did not fulfill the requirements in completing the form or they were discharged too early to complete the form. The remaining 433 cases were suitable for evaluation. Of these 433 patients, 216 received tablet "A" (the placebo) and 217 received tablet "B" (the drug).

The third postpartum day was selected to evaluate the symptoms. It was considered that a 3 day dosage of the drug would supply an adequate therapeutic level and provide a fair trial. The results obtained are illustrated in Table I.

Comment

There were approximately equal numbers of median and mediolateral episiotomies in each group. Therefore, any difference in pain severity due to the type of episiotomy was eliminated. We gave the patients a list of many symptoms to evaluate, and told them that these pills were being used to see if any of the symptoms were affected.

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**Orenzyme contains trypsin, 68 per cent, chymotrypsin, 30 per cent, equivalent to proteolytic activity of 20 mg. of crystalline trypsin.*

Table I. Third postpartum day

Severity of symptoms	*Tablet "A" (placebo)*		*Tablet "B" (drug)*	
None	30	(13.9%)	40	(18.4%)
Mild	106	(49.1%)	96	(44.2%)
Moderate	62	(28.7%)	62	(28.6%)
Severe	18	(8.3%)	19	(8.8%)

We feel that in this way no emphasis was placed on episiotomy pain.

No significant untoward reactions to the drug or the placebo were encountered.

Summary

1. A double-blind study of the influence of an enzyme preparation on pain associated with episiotomy was conducted on 500 postpartum patients, 435 of whom were suitable for final evaluation.

2. The degree of pain reported by patients receiving the test drug was not different from that reported by patients receiving a placebo.

3. Orenzyme is apparently of no value in reducing episiotomy pain.

We wish to thank the physicians and nurses of the Obstetrical Department of the Mansfield General Hospital for their cooperation, and the National Drug Company for its generous supply of Orenzyme and the placebo.

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A new method of postpartum and postoperative perineal care

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PERINEAL hygiene is of direct medical concern in the care of postpartum patients and in the treatment of lesions involving the perianal and genital region. It is acknowledged that urine, vaginal discharges, and residual fecal material may contaminate the area and impede wound healing. With the advent of "do-it-yourself" early ambulation the elaborate ritual of bedside perineal hygiene has nearly become a lost art. A poor substitute has been the application and reapplication of ointments, sprays, and medicated dressings, oftentimes to soiled tissues. Cleansing and drying of the anal and vulval regions in patients with local lesions or disease has always been a problem because of pain and tenderness. The advantages of using a warm air blower for drying perineal wounds has been cited by Counseller and Welch.[1]

Material

This report concerns the efficacy of a new automatic toilet appliance (Fig. 1) which contains mechanisms for washing the anal and vulval regions with warm water and then drying these areas by a flow of warm air. This appliance has been devised to replace the conventional toilet seat and is easily attached to any standard toilet bowl.[2] It does not require extra floor space, extensive remodeling, or additional plumbing connections. All mechanisms for operating the appliance and for heating the water and the air are contained within its hollow plastic shell. The supply of water is obtained through a simple pipe connection into the cold water inlet to the tank or flushing mechanism. Power for operating the unit and for heating the water and air is obtained through a plug connection into the nearest 110 volt, 60 cycle AC electric outlet. All electric switches, wiring connections, fan motor, and heating elements are fully insulated. The heating element for the water is thermostatically controlled so that the water spray is released at near body temperature, 94° F. There is no danger of discomfort from either excessively hot or excessively cold water or air. Both the water and air are heated instantaneously on operation of the manual controls. The force and temperature of the water spray are adjustable. A vacuum breaker in the water line prevents contamination of the water supply in the event of reverse suction. The appliance may be raised and lowered the same as a conventional toilet seat with the additional advantage of friction hinges that prevent sudden falling and jarring of the apparatus against the toilet bowl. If desired, a douche nozzle can be attached to the spray outlet by an adapter with rubber tubing. The latter attachment was not used in this study.

To evaluate the cleansing effect during the puerperium such an automatic toilet appliance (Washex) was installed in the lavatory for the obstetrical ward patients. Patients were usually ambulatory within 12 hours following delivery and remained in the

From The Obstetrical Service, St. John's Hospital, Santa Monica, California.

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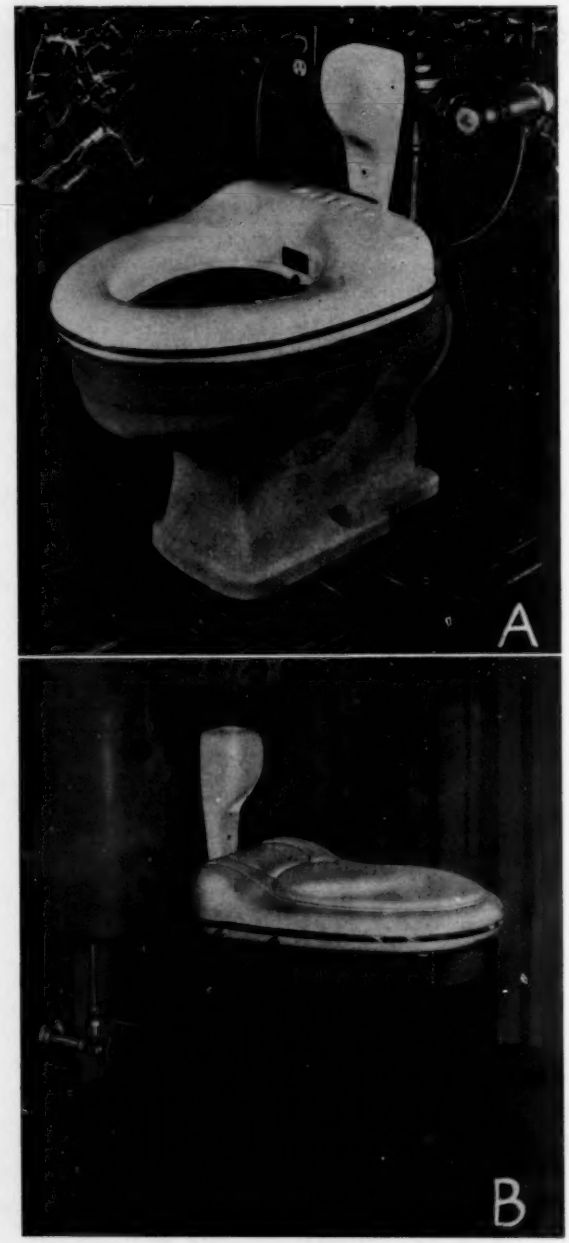

Fig. 1. *A,* Hospital, and *B,* home installation of the automatic toilet appliance. The connection to the cold water inlet, the electrical plug, and the button controls on the side of the seat are shown.

hospital from 3 to 5 days. All patients on the ward used the appliance.

Methods

Two methods of observing the effectiveness of the automatic toilet appliance were employed. First, in 25 patients comparative anal cultures were taken after regular tissue cleansing and again after water and air cleansing. Second, the obstetrical resident personally surveyed 100 patients and completed a questionnaire covering the type of delivery, parity, and complications as well as the patient's opinion of the appliance in reference to comfort, effectiveness, facility of use, presence or absence of pain, and comparison with previous methods of cleanliness.

Results

Perianal cultures. In every one of 25 cultures taken from the perianal area after Washex cleansing there was a marked reduction in the number of bacterial colonies as compared with thorough tissue cleansing (Fig. 2).

Questionnaire. All of the 100 patients were satisfied that the apparatus was effective for both cleansing and comfort. Eighty-four of the 100 patients were enthusiastic about this new method of perineal cleansing (Fig. 3). Sixteen observed a personal need for a minor adjustment of either the force or temperature of the water spray, but otherwise were satisfied. Twenty-six patients were primiparas and 74 were multiparas. Sixty-five had episiotomy and 5 had minor perineal lacerations. Twenty-one had hemorrhoids sufficient to deserve comment. All the patients who had an episiotomy had prompt and uncomplicated healing.

Comment

The nursing staff reported that the availability of the apparatus to the postpartum patients eliminated almost all of the perineal nursing care. The only change found desirable over normal usage of the automatic toilet apparatus was a reduction in the force of the water spray by means of a simple pressure adjustment for those patients who had a surgical procedure.

Patients who had one or more previous deliveries reported a most favorable comparison over previous techniques for perineal hygiene.

Several patients with postoperative urinary retention observed that the flow of warm water against the perineum was of aid in initiating urination, thus avoiding the neces-

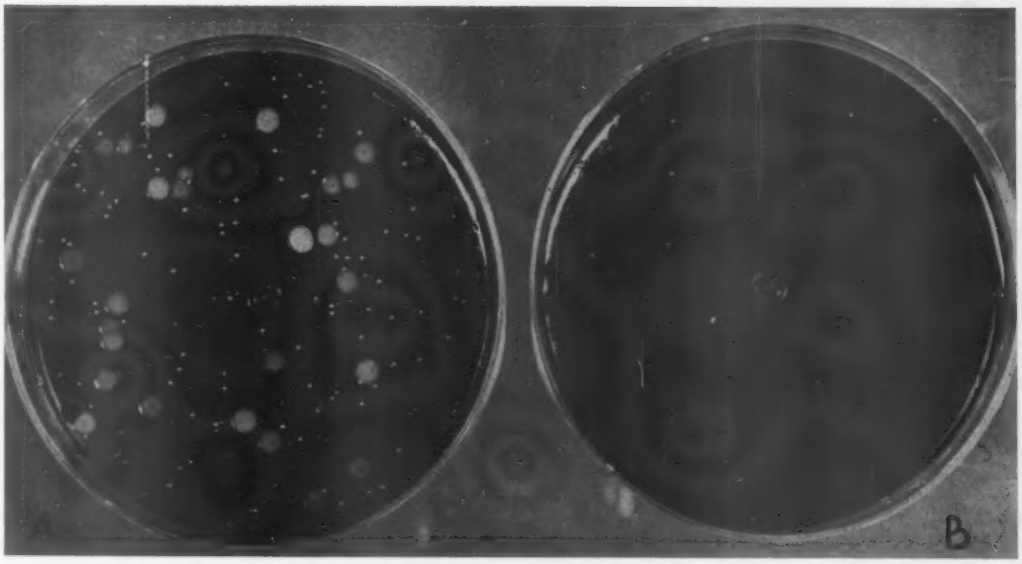

Fig. 2. *A,* Representative eosin–methylene blue agar culture of anal smear made after cleansing with tissue; *B,* after cleansing with the automatic toilet appliance.

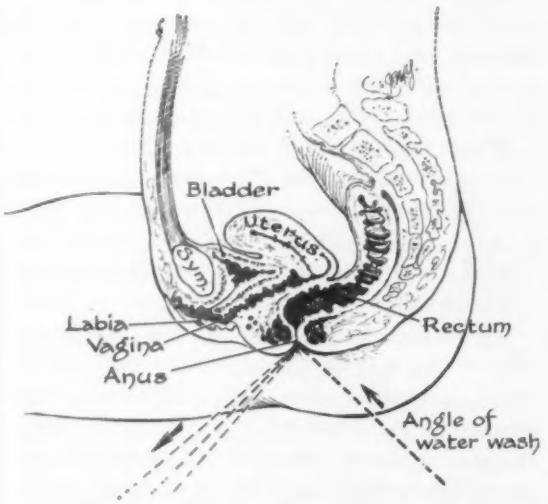

Fig. 3. Diagram showing direction of water wash of anal area. Note that the vaginal area is ordinarily at a higher level and can be washed only by leaning forward or sitting on the seat in the reverse position.

sity of catheterization. Some constipated patients pointed out that the relaxing and soothing effect of the warm water spray on the perineum helped to promote evacuation, thereby sometimes avoiding the need for an enema or rectal suppository.

Summary

The automatic toilet appliance provides an improved, efficient method of perineal care substantiated by bacteriologic studies, rapid uncomplicated healing, and less bedside nursing time. Contact of healing tissues by cotton batting or toilet tissue to remove excretions and secretions was eliminated and increased comfort was observed.

We wish to thank Dr. Klaus Butterman for his help in conducting the survey. Equipment for this study was supplied by the Washex Corporation, Santa Monica, California.

Addendum. Since this paper was submitted, over 400 additional patients have been surveyed with the same continued satisfactory results.

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Postpartum infarction of the colon in ulcerative colitis

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IT HAS been recognized that in some cases pregnancy has a deleterious effect upon the course of chronic idiopathic ulcerative colitis, but the reason for this adverse effect has not been established.[1-3] Often the exacerbation related to pregnancy or the postpartum state is of the acute fulminant variety. In these cases there is apt to be gross distention, particularly of the transverse colon. This is felt to be a dangerous complication, threatening perforation because of ischemic necrosis of the bowel wall.

The following is a case report of a patient with the very unusual lesion of infarction of the transverse colon occurring as an acute abdominal emergency post partum in a patient in whom ulcerative colitis exacerbated severely during the last month of pregnancy.

Case report

This was the first admittance to Massachusetts General Hospital of a 23-year-old white housewife who had been transferred from the Boston Lying-in Hospital because of shock, ileus, and active ulcerative colitis.

Six years before admission the patient sustained several vague episodes of nausea and vomiting, bleeding "hemorrhoids," and pain in the right lower abdomen radiating through to the back, which were treated symptomatically. Two years before entry she had a period of some 6 months of intermittent nausea, vomiting, epigastric cramps and aching pain, flatulence, and bloating. Off and on she had a mushy diarrhea, sometimes with red blood, but no pus. A year and a half before admission, x-ray examinations of the colon, upper gastrointestinal tract, and gall bladder were reported as negative. A year prior to admission bleeding hemorrhoids were diagnosed by proctoscopy. During the 2 years prior to admission and following her marriage she had gained 40 pounds to reach a weight of 208 pounds.

She became pregnant for the first time in July, 1958. There was no flare-up in the diarrhea, but there was some increase in rectal bleeding. Beginning in the seventh month, however, severe diarrhea recurred. There were up to 20 stools per 24 hours, occurring both day and night, with considerable bright red blood and mucus in the stool. The baby was active, and despite the symptoms the patient was apparently not so ill as to concern her physician.

However, with an estimated date of confinement of May 9, 1959, bleeding from the vagina began on March 7 and the patient was admitted to another hospital. The vaginal bleeding did not stop on conservative treatment and since she was rapidly going into shock she was transferred the next day to the Boston Lying-in Hospital where a stillborn child was born after spontaneous labor. The placenta had obviously separated prematurely and was infarcted and thickened to some three times its usual diameter. There were no abnormal fibrinolysins present. Transfusions

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of 3,000 ml. of whole blood restored the blood volume.

On March 9, the first postpartum day, a bloody diarrhea ensued and ecchymoses were noted at the sites of injections and venipunctures. By March 11 there was minimal jaundice (serum bilirubin, 3.2 mg. per cent) and a Bromsulphalein retention of 31 per cent. Blood nonprotein nitrogen was 70 mg. per cent. On proctoscopy there was a severe, active ulcerative colitis with many small bleeding ulcers filled with yellow mucopurulent exudate, gross friability, marked edema with total loss of normal vascular and valvular pattern, and copious quantities of pus welling into view. Because of the acute nature of the rectal process, the past history of bloody diarrhea, and the postpartum state, cortisone was prescribed along with supplemental potassium chloride. The next day the serum potassium was only 2.6 mEq. per liter; 12 hours later, after therapy, the value had risen to 3.5 mEq. per liter. There was generalized abdominal pain, fever, and a leukocytosis of 14,000 at that time, but the abdomen was not distended, and there was good peristalsis.

Early the next morning (fifth postpartum day) the patient vomited about 100 ml. of dark, changed blood. Following this, the abdomen became quiet and distention ensued. The hematocrit determination did not change from 38 per cent following transfusion of 250 ml. of blood. Because of the hematemesis the cortisone was stopped after only 200 mg. had been given.

Early that afternoon the patient was hypotensive, pale, and sweaty with a blood pressure of only 60/40 in the Trendelenburg position. She had had no bloody stools since the previous day and the hematocrit determination remained stable. X-ray examination showed no free air in the abdomen. There was a tender area above and to the right of the umbilicus with generalized rebound tenderness. Levin tube drainage was instituted, no blood being found in the aspirate at this time; she was given transfusions and there was a rather rapid improvement in her general condition over the next 4 hours. She was then transferred to the Massachusetts General Hospital.

On admission, physical examination showed an obese, pale, well-hydrated woman with no evidence of shock or pain. The temperature was 99.4° F., pulse 120, blood pressure 130/90. There were multiple ecchymoses on the skin, both at the site of injections and cut-downs and over apparently nontraumatized areas. There was a scant spotting of old blood from the vagina. There was no icterus of the skin or sclerae. There was a soft tympanitic distention of the abdomen with moderate guarding along the right side of the abdomen. Rebound tenderness was moderate and greater on the right side where there was vaguely localized tenderness. A rare peristaltic tinkle was heard. There were no masses, costovertebral angle tenderness, hepatosplenomegaly, or evidence of ascites. Two external hemorrhoids were present and not bleeding.

Past history revealed an episode of jaundice at age 4 or 5 which was poorly recalled, an appendectomy and bilateral partial oophorectomy in 1954, and evidence of late summer hay fever for several years. Family history included rheumatic fever in one sibling and cystic fibrosis of the pancreas in another sibling's child.

The initial diagnosis was an intra-abdominal surgical emergency without perforation, of unknown type, probably related to localized peritonitis due to active chronic ulcerative colitis.

Laboratory findings included a hematocrit determination of 40, white count of 36,600, with 62 per cent polymorphonuclear leukocytes, 14 per cent band forms, 13 per cent lymphocytes, 11 per cent monocytes, and normal platelets on smear. The catheterized urine had a pH of 5.0, a specific gravity of 1.015, 2-plus protein reaction, no sugar or bile, many red blood cells, and rare coarsely granular casts. Bleeding time, clotting time, and clot retraction time were normal, and there was no lysis of the clot in 4 hours. The nonprotein nitrogen level was 62 mg. per cent. Serum electrolytes were sodium 125 mEq. per liter, potassium 3.9 mEq. per liter, chloride 90 mEq. per liter, and carbon dioxide 22 mEq. per liter. Prothrombin time was 80 per cent. The serum bilirubin level was 1.4 mg. per cent, 0.9 mg. per cent being direct-reacting. Serum amylase was slightly elevated; alkaline phosphatase was normal. Plain films of the abdomen revealed a gas shadow in the right midabdomen which gave the impression of air in the biliary tree as well as small amounts of air in both the small bowel and the entire colon. The question of a biliary-duodenal fistula and gallstone ileus was raised.

The patient was treated with continued nasogastric suction, intravenous fluids and potassium, and chloramphenicol. The next morning the abdomen was slightly softer but still tender on

the right. She had had scanty bloody diarrheal stools with a few clots three times during the night. Gastric aspirate was guaiac negative, and there was no further bleeding elsewhere. The white count had fallen to 28,000, and her temperature to 99° F. Repeat x-ray studies showed a high diaphragm and a similar gas pattern.

On the morning of operation coagulation studies revealed no fibrinolysins, and the fibrinogen level was 150 mg. per cent. A thrombin titer was deficient, probably abnormal due to insufficient fibrinogen. The platelets, plasma, and serum all performed normally in a thromboplastin generation test which was interpreted to exclude poor platelet function, a circulating anticoagulant, or depressed coagulation factors.

Laparotomy was performed on the afternoon of the sixth postpartum day. Under endotracheal oxygen-cyclopropane anesthesia the abdomen was opened. About 4,000 ml. of thin, bloody peritoneal fluid was found. The entire large bowel appeared cyanotic and of doubtful viability, especially the transverse colon where hemorrhage into its wall with hematomas had thickened the bowel. The biliary tract appeared normal. The decision was made to perform a subtotal colectomy and ileostomy. The bowel, on resection, was found to have a "porky" induration. Veins overlying the transverse colon and in the nearby omentum in the distribution of the entire midcolic vein were thrombosed with very dark red clot, so that there was no bleeding from their transection. There had been no obvious perforation of the colon, and the uterus did not appear unusual considering its postpartum state.

The next day the patient's hematocrit determination was 40 and NPN 65 mg. per cent. The stomas of ileum and sigmoid had a normal color, and the former was functioning. Except for some postoperative atelectasis and difficulty with respiratory secretions the patient did quite well with a falling white blood count and NPN. By the second postoperative day the blood fibrinogen level was 380 mg. per cent. No postoperative jaundice developed. On the fourth postoperative day the clamp was removed from the exteriorized end of the sigmoid.

On the twelfth postoperative day she showed evidence of a coliform wound infection around the sigmoid mucous fistula. This cleared with removal of the stay sutures and the use of compresses to the laid-open area. She rapidly regained an appetite, and her weight stabilized at 185 pounds. There were relatively few and scanty rectal discharges of mucopurulent material with some old blood and she was discharged home on the twenty-sixth postoperative day.

The patient has been followed now for 6 months and no evidence of postpartum pituitary insufficiency or liver dysfunction has developed. The patient is managing the ileostomy well and the sigmoid fistula and rectum are quiescent. Her present weight is 209 pounds.

Pathology. The wall of the ascending colon measured up to 4 mm. in thickness. The internal surface was pink and showed multiple superficial irregular ulcerations measuring up to 7 mm. in diameter in the cecum. The remaining colon measured from 8 to 12 cm. in circumference, and its wall was 4 to 10 mm. in thickness. A 30 cm. length of the transverse colon was dark red and obviously infarcted with irregular and superficial necrosis of the mucosa. There were multiple rounded confluent ulcerations measuring up to 25 mm. in diameter. The ileum and ileocecal valve appeared entirely normal. The diagnosis was ulcerative colitis with diffuse venous and arteriolar thromboses, organizing and fresh, with hemorrhagic infarction of the transverse colon. Arteriolar thromboses were organizing in the hilar vessels of mesenteric lymph nodes. The colon had the typical changes of ulcerative colitis, and the ileum was normal microscopically.

The pertinent autopsy findings on the baby showed that the infant weighed 1,600 grams, had a crown-rump length of 27 cm., and was an early macerated premature female. It had generalized congestion, and there were hemorrhages in the epicardium, myocardium, and interstitially in the lungs.

The placenta weighed 685 grams (approximately twice the expected weight for this gestational age). It measured 19 by 16 by 4 cm. (normal thickness, 2 cm.). The cord was markedly edematous, as was the placenta itself. The fetal surface of the latter was turgid and glistening with fluid. The intervillous space was extremely hyperemic, with numerous intervillous thrombi of recent nature. Histologically, the intervillous space was engorged with blood and fresh thrombi, as were the vessels of the decidua. Many areas showed early degeneration. There were no old infarcts or other changes suggestive of toxemia of pregnancy, abruptio placentae, or arteriosclerosis.

Comment

This vascular accident occurring in ulcerative colitis is being reported because of its unusual nature rather than because of any understanding of the mechanism involved. Fibrinolysins attendant upon placental disease or thrombotic phenomena due to circulation of amniotic fluid contents in the maternal vascular system would not seem to have played a role here. The patient was in severe shock prior to delivery. The question has arisen as to whether this in itself led to intravascular thrombosis, which in turn led to a deficiency of fibrinogen and perhaps a hemorrhagic state. It is of some interest, therefore, that the bloody diarrhea resumed the day after delivery along with ecchymoses into the skin, but the acute episode of hematemesis, ileus, and shock did not occur until the fifth postpartum day, some 36 hours before the laparotomy.

Another possible hypothesis is that there were alterations in the blood coagulation system induced by bacterial endotoxins which led to a generalized and gradual deposition of "hyaline thrombi" in small vessels.[4] Such a mechanism might better explain the widespread involvement—the urinary changes (although these might have been due to shock), the abnormal serum bilirubin, and Bromsulphalein retention, the skin ecchymoses, and the hematemesis, as well as the infarction of the colon. Such a generalized Shwartzman reaction might have been triggered by the repeated absorption of endotoxins from the septic and permeable colon. Another mechanism for producing disseminated intravascular thrombosis is the injection of incompatible blood, but there is little evidence to suggest its applicability in this case.

The prompt colectomy here seemed to save this woman's life, and her reaction to the operation was immediately favorable. Certainly the transverse colon had become nonviable.

One wonders whether what happened here in the extreme may be causally related to the de novo onset or the exacerbation of ulcerative colitis in the postpartum period. Often such cases are severe and run prolonged, difficult courses.

Summary

The case report of a young woman who required postpartum subtotal colectomy for infarction of a colon severely involved with ulcerative colitis has been presented.

We wish to acknowledge the enthusiastic interest and help of Donald G. McKay, M.D., and the contributions of Kurt Benirschke, M.D., for the pathological studies carried out on the fetus and placenta. We wish also to express our appreciation to Marshall K. Bartlett, M.D., and Duncan E. Reid, M.D., for their help in the clinical management of this problem.

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Postpartum intestinal obstruction following vaginal delivery

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POSTPARTUM intestinal obstruction following vaginal delivery usually involves the small bowel. The typical signs and symptoms may be obscured by the size of the uterus or by other complications resulting from pregnancy. This may lead to confusion, delay in diagnosis, and a fatal result.

Numerous reports of intestinal obstruction occurring during the antepartum period or following cesarean section have appeared.[1-4] There has been a paucity of reports dealing with it during the postpartum period following normal vaginal deliveries. During the past 5 years at the Methodist Hospital of Brooklyn we have had 4 such cases.

Two cases followed premature deliveries and 2 occurred after term deliveries.

Case 1. A 23-year-old white woman, para i, gravida ii, blood type A, Rh negative (husband, Rh negative), Wassermann negative, whose expected date of confinement was May 6, 1953, was admitted to the Methodist Hospital Feb. 3, 1953, complaining of constant abdominal pain of 12 hours' duration, with intermittent vomiting. Past history revealed a normal delivery in 1949 and an appendectomy later that same year. Examination upon admission revealed a temperature of 98° F., pulse 76, respirations 16, blood pressure 108/60. Abdominal examination revealed tenderness in the right upper quadrant. There was also right costovertebral angle tenderness. Rectal examination showed the fetal head to be unengaged and the cervix closed and uneffaced. Tentative diagnoses were: (1) possible right pyelitis, (2) threatened abortion at 6 months.

Laboratory data on admission were: red blood cells 3.8 million, hemoglobin level 11 Gm., white blood cells 16,950, with a differential of polymorphonuclear white cells 98 per cent, lymphocytes 2 per cent, and normal catheterized urine. Sedation and an infusion were given. A genitourinary consultant at this time found right costovertebral angle tenderness and advised cystoscopy. Twenty-four hours after admission the white blood cells were 18,700 with polymorphonuclear white cells 84 per cent and lymphocytes 15 per cent. Blood nonprotein nitrogen was 27 and blood sugar 89. Forty-eight hours after admission cystoscopy was performed and a No. 6 catheter passed to the right pelvis encountered a complete obstruction at the 20 cm. mark and intravenous pyelogram showed a definite obstruction of the right renal tract. An indwelling catheter was left in the right ureter. The following day at 2:30 A.M. labor began and the patient was delivered of a 2 pound, 15 ounce live male by assisted breech extraction at 2:45 A.M. Twelve hours later the abdomen was markedly distended and tender throughout. No rigidity was present. The uterus could be felt about 4 fingerbreadths above the symphysis. The impression was paralytic ileus. Red blood cells were 5.2 million, hematocrit determination 45, hemoglobin level 13.9 Gm., white blood cells 31,600, with a differential of polymorphonuclear white cells 99, lymphocytes 1. On the second postpartum day there was no improvement in distention and tenderness and rebound tenderness were more marked. A hard tender mass

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was outlined in the right lower quadrant. A flat plate of the abdomen revealed the typical signs of a small bowel obstruction. An exploratory laparotomy was performed revealing a volvulus caused by an adhesive band resulting in a large portion of gangrenous small bowel. The band was transected and a resection of the small bowel performed. The patient had an uneventful recovery.

Case 2. A 23-year-old white woman, para i, gravida i, blood type B, Rh positive, Wassermann negative, was admitted to the emergency room of the Methodist Hospital Dec. 8, 1954, in severe shock with shallow infrequent respirations, absent pulse, no blood pressure, and vomiting "coffee ground material." She died 20 minutes after admission to the emergency room. Past history revealed that 11 months previously an exploratory laparotomy and appendectomy had been performed. She had an uneventful postoperative course and was discharged 10 days later. Three weeks prior to the present admission the patient had been delivered by low forceps of a live female infant weighing 7 pounds, 14 ounces. She had a normal postpartum course and was discharged in 5 days. She was well until 3 days before admission when she suffered severe epigastric pain and cramps. A local doctor diagnosed food poisoning. She continued to have abdominal pain, nausea, vomiting, weakness, and nervousness. The day prior to admission she received 2 doses of pentobarbital sodium 0.045 Gm., and meperidine 50 mg. On the day of admission the family brought her to the hospital by ambulance. At autopsy, "the terminal ileum for a distance of about 3 feet was red and edematous. The mesentery of this portion of the intestine was reddish, edematous, and hemorrhagic. The changes in the intestinal wall were sharply demarcated about 4 mm. from the ileocecal valve. This segment of the intestine had entered a hole made by the mesentery of the terminal ileum and a band of fibrous tissue from the stump of the appendix to the root of the mesentery. The hole hardly accepted an index finger, and through it the distal segment of the ileum was herniated and strangulated."

Case 3. A 28-year-old white woman, para 0, gravida i, blood type O, Rh positive, Wassermann negative, whose expected date of confinement was July 20, 1957, was admitted to the Methodist Hospital April 28, 1957, complaining of abdominal pain of 6 hours' duration. Past history revealed an appendectomy in 1944. Her antepartum course had been normal until 12:15 A.M. April 28, 1957, when she noticed a knife-like diffuse abdominal pain confined mostly to the right upper quadrant. She vomited once. A normal bowel movement had occurred the previous day. On admission at 6:15 A.M. April 28, 1957, the temperature was 97° F., pulse 76, respirations 22, blood pressure 106/68, and the uterus was tender and enlarged to the size of a 6½ months' pregnancy. Fetal heart rate was 140 in the left lower quadrant. There was no vaginal bleeding. At 10:15 A.M. the patient complained of pain over the fundus and the uterus appeared larger than expected. A diagnosis of abruptio placentae was made.

Laboratory data at this time revealed a hemoglobin level of 12.5 Gm., white blood cells 17,600, with a normal differential and a normal urinalysis. The membranes were ruptured artificially at 11:30 A.M. At 8:15 P.M., a live premature male infant was delivered precipitously; and the expressed placenta revealed about 150 c.c of old blood. The patient was returned to her floor 1½ hours after delivery and appeared normal at this time. Blood pressure was 120/80, pulse 88, uterus firm and bleeding normally. Three hours after delivery the patient complained of "severe after pains" according to the nurse's notes and was given codeine, 0.06 Gm. Five and one-half hours after delivery aspirin, 0.3 Gm., was given again by the nurse for "after pains." Nine hours after delivery she was still complaining of pain and codeine 0.06 Gm. and aspirin 0.06 Gm. were repeated by the nurse for "after pains." Ten and a half hours after delivery she complained of being unable to breathe, was cold, clammy, apprehensive, and uncomfortable. She had been unable to void but on catheterization only 125 c.c. of urine was obtained. Her blood pressure was 80/50, pulse rate 124. The nurse noted that the abdomen was distended and very tender. She was returned to the delivery floor pale, with blood pressure 80/30, pulse rate 130, and a very tender midline mass 3 fingerbreadths above the umbilicus was noted. There was no external bleeding. The abdomen was markedly tender with rebound tenderness. Nothing could be expressed from the uterus and a diagnosis of shock due to intra-abdominal bleeding was made. Pelvic examination revealed that the uterus could be sounded to 5 inches in depth which was not the height of the mass. The uterus could not be separated from the mass. An exploratory

Table I. Reported cases of postpartum intestinal obstruction following vaginal delivery

Author	*Day of obstruction*	*Previous operation*	*Lesion*	*Operation*	*Result*
1. Spence[5]	1	Yes	Volvulus of cecum	None	Died following spinal anesthesia
2. Weintraub and Jaffe[1]	1	No	Congenital adhesive band	Release of band; cecostomy	Recovered
3. Sheldon[6]	3	No	Volvulus of cecum	Reduction of volvulus; cecostomy	Recovered
4. Henkin[7]	2	No	Congenital adhesive band	Release of band; appendectomy	Recovered
5. Bellingham, Mackay, and Winston[8]	10	Yes	Adhesive band	Release of band	Recovered
6. Woodruff and Epperton[9]	1	Yes	Adhesive band	Release of band	Recovered
7. Amsterdam[10]	2	Yes	Adhesive band	Resection of gangrenous loop of ileum	Recovered
8. Bollinger and Fowler[11]	12	Yes	Strangulated small bowel due to bands	None: treated conservatively for parametritis and peritonitis	Died
9. Hilton and McGinnis[12]	4	No	Compound volvulus of sigmoid and ileum	Resection of ileum detorsion of sigmoid	Recovered
10. Smith[13]	3	Yes	Adhesive band	Release of band	Recovered
11. Smith[13]	21	Yes	Adhesive band	Release of band	Recovered
12. Noonan and Harper[14]	7	Yes	Adhesive band	Release of band	Recovered
13. Noonan and Harper[14]	21	Yes	Adhesive band	Release of band	Recovered
14. Laufe and Meyers[15]	2	Yes	Volvulus of ileum	Resection of ileum and ileotransverse colostomy	Died
15. Laufe and Meyers[15]	2	Yes	Intussusception of terminal ileum into colon	Ileocolic resection	Recovered
16. Laufe and Meyers[15]	1	Yes	Volvulus of cecum	Resection of cecum; ileotransverse colostomy	Recovered
17. Laufe and Meyers[15]	1	Yes	Segmental ileus	Cecostomy	Recovered
18. Sargent, Adams, and Westfall[16]	1	Yes	Ovarian tumor	Oophorectomy	Recovered
19. Mansell and Beil	1	Yes	Adhesive band; volvulus	Resection of terminal ileum and colon; lateral anastomosis of ileum to colon	Recovered
20. Mansell and Beil	22	Yes	Adhesive band; volvulus	None	Died on admission
21. Mansell and Beil	1	Yes	Adhesive band; volvulus	Resection of ileum	Recovered
22. Mansell and Beil	9	Yes	Adhesive band	Release of band	Recovered

laparotomy was performed. There was ecchymosis of the left cornu of the uterus, the site of the previous abruptio placentae. The mid-portion of the small bowel measuring about 8 feet in length was black and gangrenous, its mesentery ecchymotic. A volvulus under and around a violin string–like adhesion arising from the previous appendectomy was noted. There was approximately 2 feet of viable small bowel from the ligament of Treitz proximally and another 2 feet of viable small bowel distally from the ileocecal valve. The adhesion was transected and a small bowel resection done. A transfusion of 1,000 c.c. of blood was given. The patient made an uneventful recovery.

Case 4. A 29-year-old white woman, para vi, gravida vii, blood type O, Rh positive, Wassermann negative, was admitted to the Methodist Hospital May 17, 1957, complaining of abdominal pain. Past history revealed an appendectomy in 1945 and an exploratory laparotomy and closure of wound to to an accidental stab wound in 1956. Nine days prior to admission she had a normal vaginal delivery of a live full-term infant, a normal postpartum course, and was discharged on the fifth postpartum day.

The patient stated she was well until the day before admission when she began to have intermittent abdominal pain, "like labor cramps," nausea, and frequent episodes of vomiting. She had not had any bowel movement for 2 days and had urinary frequency and dysuria. Examination on admission revealed a temperature of 99.4° F., pulse 72, respirations 20, blood pressure 130/95. Abdominal examination revealed right upper and lower quadrant scars, soft distention, tenderness in the lower abdomen, and no bowel sounds. Pelvic examination revealed the uterus to be halfway to the umbilicus. The impression was: (1) intestinal obstruction and (2) cystitis.

Laboratory data on admission were: hemoglobin 13.5 Gm., white blood cells 15,000, polymorphonuclear cells 94, lymphocytes 6; catheterized urine, 25 to 30 white blood cells with 1 to 3 clumps, and 18 to 20 red blood cells per high-power field. A flat plate of the abdomen revealed evidence of a dilated loop of small bowel in the left lower quadrant. An exploratory laparotomy revealed a ringlike adhesive band obstructing 2 feet of ileum. The distal end of the obstruction was about 1 foot from the ileocecal valve. The band was transected and the patient made an uneventful recovery.

Comment

Postpartum intestinal obstruction following vaginal delivery is rare. In the past 5 years in the Methodist Hospital of Brooklyn there were 4 cases in 11,832 vaginal deliveries—an incidence of 1:2,958 vaginal deliveries.

Table II. Types of previous operation

Appendectomy	12
Appendectomy and later exploratory laparotomy for stab wound	1
Suspension of uterus and appendectomy	1
Left salpingo-oophorectomy and appendectomy	1
Salpingectomy and 1 year later appendectomy	1
Cholecystectomy	1
Ileotransverse colostomy and later cholecystectomy	1
Total	18

Table III. Onset of symptoms following delivery

Within 24 hours	8
2nd postpartum day	4
3rd postpartum day	2
4th postpartum day	1
7th to 22nd pastpartum day	7

Table IV. Lesion found at time of obstruction

Adhesive band	9
Volvulus	5
Adhesive band and volvulus	3
Congenital band	2
Intussusception	1
Ileus	1
Ovarian tumor	1

Table V. Mortality

Spence[5]	Died following spinal anesthesia
Bollinger and Fowler[11]	Mistaken diagnosis; treated conservatively for parametritis and peritonitis
Laufe and Meyers[15]	Died 12 hours postoperatively after progressive downhill course
Mansell and Beil	Mistaken diagnosis; died 20 minutes after admission to emergency room

A perusal of the English literature during the past 20 years reveals sporadic reports in this regard. No doubt numerous other cases have occurred but were not reported.

To date, including our 4 cases, 22 cases have been reported (Table I).

Pathogenesis. It has been suggested[13] that postpartum intestinal obstruction is produced by a herniation of the small bowel through a window created by a band of adhesion at the site of the previous operation, with the band extending between the appendectomy scar and the posterior peritoneum. The enlarging uterus stretches the band by pushing the bowel higher in the abdomen. Following delivery with the sudden reduction of intra-abdominal pressure and with the rapid diminution of the large uterus, a loop of small bowel may easily be drawn through this window and by its peristaltic action more and more becomes involved with possible strangulation as a result.

Types of previous operation. That the role of previous operation is an important one in the etiology is obvious by the fact that 18 of the 22 patients had previous laparotomies (Table II). It is interesting that only 1 obstruction occurred after a suspension of the uterus and that patient had had an appendectomy also. Previous appendectomy appears to be the most common cause. It alone is noted prior to 12 of the cases and in conjunction with 4 other operations. All our 4 patients had previous appendectomies.

Onset of symptoms following delivery. (Table III). The majority of the cases occurred during the first 4 days with over one third during the first 24 hours. It is during this time that the uterus is still large and may confuse the diagnosis. In our Case 3, the abdominal pain was attributed by the nurse to "after pains."

Lesion found at time of obstruction. (Table IV). It would seem that a band of tissue obstructing the bowel is the most frequent cause of postpartum intestinal obstruction whether it results in the formation of a volvulus, an adhesive band, or is purely congenital. It is interesting to note that of the 4 cases of the 22 that did not have previous operation, 2 were due to congenital bands and 2 to volvulus without congenital bands. The sudden readjustment of the bowel to the rapidly involuting uterus unquestionably plays a major role, but this occurs only if there is some aperture through which the bowel is drawn.

Mortality. In the 22 cases reported, there were 4 deaths. However, of the 4 deaths (Table V), only 3 could be attributed to the complication since the first case reported in 1937 by Spence[5] was attributed to anesthesia.

Pain, vomiting, and the failure to pass flatus or feces, the well-known essentials of obstruction, may be forgotten in the postpartum vaginal delivery patient, since these symptoms are common. However, sudden, severe, continuous, or colicky pain out of proportion to "after pains," followed by vomiting should make one suspicious. Once obstruction is suspected, delay for the purpose of making an accurate diagnosis should not occur. Prompt surgical intervention must be contemplated, supported by Wangensteen suction-siphonage and infusions. Delayed diagnosis as well as indecision and unreasonable conservatism may end disastrously. In our Case 2, there is no doubt that an incorrect diagnosis was responsible for the patient's death.

Summary

1. Four cases of postpartum intestinal obstruction following vaginal delivery have been added to the literature, making a total of 22 cases reported.

2. The incidence in the Methodist Hospital of Brooklyn for the past 5 years has been 1:2,958 of the vaginal deliveries.

3. Previous operation is an important etiological factor, responsible for 18 of the 22 cases reported. Previous appendectomy was the most common cause, responsible definitely for 12 cases and possibly for 4 others.

4. The sudden readjustment of the bowel to the rapidly involuting uterus unquestionably plays a major role but this occurs only if there is some aperture through which the bowel is drawn.

5. The majority of cases appeared during the first 4 days with over one third during the first 24 hours post partum.

6. Three of the 4 deaths due to intestinal obstruction after vaginal delivery could be attributed to this complication.

7. Prompt investigations of abdominal symptoms in the immediate postpartum phase following vaginal delivery and early definitive treatment are necessary. Indecision and conservatism are dangerous.

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Diagnostic conization of the cervix during pregnancy

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THE reported incidence of invasive carcinoma of the cervix occurring during pregnancy varies from institution to institution but is usually stated to occur about once in every 2,000 obstetric patients. Stated another way, pregnancy is said to complicate carcinoma of the cervix in about 1.5 per cent of cases. Based on these figures, an obstetrician delivering 300 babies yearly could expect to see 1 carcinoma of the cervix concomitant with pregnancy once every 7 years, or about 4 to 5 cases in a lifetime.

It is now well established that atypical epithelial changes occurring during pregnancy carry the same significance as in the gynecologic patient.[1-5] In 1958, Greene and Peckham,[6] in a review of the available literature to that time found that 90 out of 122 carcinomas in situ (73.77 per cent) diagnosed during pregnancy persisted in the postpartum period. The failure of regression of these lesions post partum has been reaffirmed by others,[7, 8] and many lesions that have supposedly regressed have been found on retrospective study to lack the necessary criteria for diagnosis.

It is universally accepted that our most accurate aid to the detection of early and preclinical carcinoma of the cervix is routine cytologic screening of gynecologic patients. The yield by cytodetection during pregnancy has been shown to equal that of gynecologic patients.[8-11] It seems inconceivable to deny this to the obstetric patient also, and indeed, as Andros[12] states, "pregnancy provides a good opportunity for cellular studies since many younger women do not present themselves for examination except during and immediately after pregnancy."

Early diagnosis of carcinoma is of particular importance during pregnancy. Survival statistics[13-15] indicate that patients in whom lesions were diagnosed in early pregnancy fared better than those with lesions of comparable clinical stages diagnosed in late pregnancy or the puerperium. Prior to the third trimester patients who survived 5 years might not have differed appreciably from the nonpregnant when the lesions were compared stage for stage, while apparent cure rates after that and in the postpartum period were poorer. Stander and Lein[16] state that the chief threat to the pregnant patient with carcinoma of the cervix is not the alteration of the biologic behavior of the neoplasm by pregnancy but the delay that may occur before the carcinoma is detected.

The diagnosis of cervical carcinoma may, in the early stages, be obscured by a normally appearing cervix. Carter and associates[10] have reviewed the clinical evaluation of 217 patients with in situ carcinoma at their clinic. In 88.5 per cent the cervical epithelium was evaluated as being benign, and malignant, or questionably malignant in

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11.5 per cent. Clinical evaluation of the cervix alone is obviously inaccurate and affirms the importance of a careful diagnostic regime for all of our patients.

Routine screening of our obstetric patients was instituted in 1958. Our cytologist reports the smears as negative, inconclusive, suspicious, or positive.

An inconclusive report may indicate normal cells, which for technical reasons are not clearly seen, or abnormal cells, which are clearly seen but are too few in number to interpret adequately. A suspicious report indicates the cytologist's feeling that the patient does have malignant changes, which are not clearly enough defined to call positive. Positive, in turn, means that there are abnormal cells which are diagnostic of carcinoma at any stage of its development from the earliest atypical hyperplasia or dysplasia through carcinoma in situ to invasive carcinoma.

In conjunction with routine cytologic screening the following procedure is followed:

1. Any lesions of the cervix that bleed or present a suspicious appearance are subjected to biopsy.

2. Spotting or bleeding during pregnancy calls for repetition of cervical inspection and possible resmear and biopsy.

3. Any patient with a positive Papanicolaou smear must have a repeat smear and four-quadrant biopsy performed. If the biopsy shows any epithelial atypia short of invasion, conization of the cervix should be done.

4. Any patient with persistently positive smears, regardless of the biopsy diagnosis, should have a conization.

5. Any patient who shows a suspicious or inconclusive smear should have repeat smears taken. Repeated abnormal smears in any combination of classes (suspicious and suspicious, suspicious and inconclusive, inconclusive and inconclusive) demand a cervical biopsy.

6. Any patient with a biopsy diagnosis of basal cell hyperplasia with atypism or carcinoma in situ or persistently positive smears should have a conization.

Biopsy diagnosis of a lesser lesion than carcinoma in situ still requires conization, since we hold that atypical hyperplasia has possible cancer precursor potentiality and is frequently coexistent with actual carcinoma. McKay and co-workers[17] showed that one third of their patients with atypical hyperplasia had associated in situ or invasive carcinoma. Progression to in situ or invasive was demonstrated in 3.8 per cent.

Some authorities recommend a superficial conization to obtain only the squamocolumnar junction. Since the malignant process often extends high in the cervical canal, we believe that conization should be just as extensive in the pregnant as the nonpregnant patient so that we may provide the pathologist with sufficient material for an accurate and reliable diagnosis.

Adequate conization has been recommended by others. Beecham and Emich[18] state that a cold knife cone must be done on all pregnant patients having Class 3, 4, and 5 smears and in those found with a biopsy diagnosis of atypia. No statistics are presented on their cases. Carter and associates[10] did conizations on 11 of 38 patients with carcinoma in situ during pregnancy. No statistics are given about the outcome of these patients, but they all had subsequent pregnancies and 4 had reconing procedures during subsequent pregnancies (of which 2 were aborted). Mussey and Soule[19] stated that, although multiple biopsies do not place the pregnant woman in jeopardy, the hazard of overlooking invasive cancer is ever present, and proof of the absence of invasion is lacking unless a conization or hysterectomy specimen is available. Holzaepfel and Ezell[13] state that, in addition to other recommended diagnostic procedures, cold knife cone may be performed but they qualify this by a recommendation against indiscriminate use of the procedure. Schmitz[20] did cone biopsy on pregnant patients with a diagnosis of preinvasive carcinoma on biopsy, 1 being made as late as the thirty-second week. Five actual invasive carcinomas were found. Of 3 patients on whom Boyd[21] performed cone biopsies during pregnancy, one, 3 months

pregnant, aborted 3 days later. He states that, when this procedure is performed during pregnancy, the cone must be limited to some extent and this has created problems related to inadequate tissue. Baker and Hawks[22] reported cone biopsies on 4 patients during pregnancy—1 aborted and 3 had term deliveries with hysterectomy later. McDuff and co-workers[23] claim that cold knife cone can be performed without interference to the pregnancy. No statistics are presented. Moore and Gusberg[7] state that cone biopsy during pregnancy is not unduly risky and is the preferred type of biopsy. They performed 22 without resulting abortion; however, this was obviously of a more superficial nature since no anesthesia was used. Offen and Ferguson[24] describe their technique for cold conization and report that this has been used over 45 times in pregnant patients. There is no discussion as to results or sequelae from the procedure.

This study was instituted in an attempt to determine if conization of the cervix during pregnancy was feasible from the standpoint of complications or interruption of the pregnancy, and if the yield of diagnoses of invasive carcinoma from the procedure warranted its use in the face of possible complications.

Material

During the years 1958 and 1959, there were 7,246 deliveries at the Kaiser Foundation Hospital in Los Angeles. The exact number of obstetric patients screened by the Papanicolaou method is currently being tabulated, but we believe that approximately 5,500 to 6,000 were screened. The only patients omitted from the screening procedure were those who had been tested within 6 months of their initial prenatal examination. A small number of patients refused to have the test for various reasons.

As a result of the screening routine a diagnosis of cervical atypia, carcinoma in situ, or invasive carcinoma of the cervix was made on 32 pregnant patients. Twenty-two patients had carcinoma in situ and 1 had actual invasion demonstrated.

This present report deals only with 16 patients who had cold knife conization of the cervix performed at varying stages of pregnancy in the 18 months' period from August, 1958, to February, 1960. Prior to August, 1958, reliance was placed on the four-quadrant biopsy for diagnosis in the pregnant patient, following an abnormal cytology report. The conizations were performed after repeated suspicious or positive Papanicolaou smears, and usually in association with cervical biopsies showing basal cell hyperplasia with atypism or carcinoma in situ.

Table I shows the comparative accuracy of biopsy and conization in 193 gynecologic patients with in situ carcinoma who had both procedures performed at our institution. This indicates that biopsy is only 61 per cent as accurate as conization. Furthermore, among 123 cases of invasive carcinoma of the cervix the diagnosis of invasion was established 16 times (13 per cent) when the biopsy diagnosis was carcinoma in situ. It has been the policy in our clinic to perform conization of the cervix in the presence of a biopsy diagnosis of in situ carcinoma in order to rule out invasion. We felt that, in order to be consistent, conization should be performed regardless of the coexistence of pregnancy. Table I shows our experience with these patients.

Age distribution of pregnant patients

The youngest patient was 24, the oldest was 38, and the average age was 29.3 years. The average age is somewhat younger than the average for all in situ carcinoma, and this simply reflects the younger age of the pregnant patients as a whole compared to gynecologic patients.

Parity

There were no primigravidas in this group. There was 1 para vi. The absence of lesions in the first pregnancy probably is related only to the general younger age rather than any effect of multiple pregnancies on the occurrence of carcinoma of the cervix.

Table I. Carcinoma in situ in gynecologic patients

Diagnostic procedure	Pathologic diagnosis	
	Atypia*	In situ
Biopsy	75	118
Conization	14	179

*Atypia includes: chronic cervicitis, 32 cases; cervical polyp, 1 case; basal cell hyperplasia with atypism, 42 cases. (As can be seen the biopsy apparently removed the entire area of in situ carcinoma in a small number of cases.)

Table II. Age distribution of pregnant patients

Age*	No. of cases
20-24	2
25-29	8
30-34	4
35-39	2

*Average 29.3 years.

Table III

Parity	No. of cases
0	0
1 to 2	8
3 to 4	6
5 and over	2

Table IV. Weeks of gestation at time biopsies and conization were performed (calculated from last menstrual period)

Weeks	Biopsy (No. of cases)	Cone (No. of cases)
2 to 4	2	-
5 to 8	1	1
9 to 12	6	1
13 to 16	5	4
17 to 20	1	7
21 to 24	1	3

Timing of conization

The earliest biopsy was done at 2½ weeks of pregnancy and the latest at 19½ weeks. The earliest conization was at 6½ weeks and the latest at 22½ weeks. The patients who had biopsies at a very early stage of pregnancy (2 to 8 weeks) had abnormal cytologic smears prior to the pregnancy, but the follow-up routine was observed during the ensuing pregnancy.

Conization in the vast majority of cases was done 1 to 4 weeks after the biopsy. In 1 case there was a 2 months' delay and in 1 additional case there was a delay of 3 months.

Appearance of cervix

The cervix was described as being normal in 7 cases and 9 times was described as showing a decidual reaction, laceration, or erosion. In no instance was there immediate suspicion of malignancy.

Relationship of smear class to ultimate diagnosis

With the exception of 2, all patients had 3 additional confirmatory smears taken simultaneously after we received the initial report of an abnormal smear. Two of the patients had still further cytologic studies. Cervical biopsies were usually taken at the time of the repeat smears. The various combinations of smear, biopsy, and cone diagnoses are shown in Table V.

The presence of a positive smear in this small group of patients was always indicative of some form of epithelial abnormality on tissue examination, and in all cases but 1 indicated carcinoma in situ or invasion. The 1 case of invasive carcinoma was diagnosed at 18 weeks and therapy instituted immediately. Had not the conization been done, this patient would, theoretically, have had an additional 22 weeks of pregnancy to propagate the carcinoma, probable vaginal delivery to disseminate it, and the puerperium during which the malignancy would further flourish before the diagnostic cone would have been done.

Complications

There were no immediate complications of conization in 14 of the 16 patients. One patient developed cramping and bleeding 16 days later, and another developed a bloody discharge 30 days later.

Blood loss was estimated in 14 patients. This varied from 30 to 400 c.c. with an average of 125 c.c. Even though most estimates of blood loss are inaccurate, the 1

Table V

No. of patients	*Smear classification*	*Pathologic diagnosis*	
		Biopsy	*Cone*
4	Suspicious; positive	3 in situ 1 BCH*	4 in situ
1	Suspicious; positive twice	1 BCH	1 BCH
4	Positive (1 smear only)	4 in situ	4 in situ
4	Positive; positive	4 in situ	3 in situ 1 BCH
1	Positive twice; negative	1 BCH	1 in situ
1	Suspicious; suspicious	1 cervicitis	1 cervicitis
1	Inconclusive; positive	1 in situ	1 invasion, early

*Basal cell hyperplasia with atypism.

Table VI. Outcome of pregnancy

	No. of cases
Normal full-term delivery	8
Cesarean hysterectomy	1
Premature labor	1
Aborted	2
Undelivered	3
Pregnancy therapeutically interrupted	1

estimate of 400 c.c. probably was fairly accurate inasmuch as the patient's hemoglobin dropped from 12.3 Gm. per cent to 11.4 Gm. per cent.

Hospitalization time averaged 2.2 days, varying from 2 to 4 days.

Adjunctive therapy

Nine patients received 500 mg. of hydroxyprogesterone caproate (Delalutin), 5 received a uterine relaxing hormone (Lutrexin), and 3 received antibiotics. Four patients received no medication except analgesics as needed.

Outcome of pregnancy

Eight patients had uncomplicated, spontaneous, or low forceps deliveries. Labor ranged from 2 to 25 hours with an average of 7 hours. The patient who had a 25 hour labor was delivered of a 9 pound, 8 ounce infant uneventfully.

One patient was delivered prematurely at 31 weeks' gestation, 8 weeks after conization. We believe it unlikely that the conization was responsible.

Two patients aborted 21 and 26 days after the cone, and we must admit that the conization may have precipitated the abortions in these cases. Percentagewise, however, they do not exceed the number of anticipated spontaneous abortions.

Three more patients are progressing normally in the last trimester, with 2 at term.

The 1 patient with invasion has had treatment involving interruption of the pregnancy.

Routinely, we allow our patients with proved carcinoma in situ to be delivered vaginally, and definitive treatment can be instituted at a later date.

The 1 cesarean hysterectomy was performed on a patient who had a conization at 22½ weeks' gestation. She was delivered at 34 weeks' gestation of a premature infant, which did not survive. Cesarean section was elected after a prolonged labor without cervical dilatation. Hysterectomy was then performed because of the combined indications of amnionitis (secondary to prolonged premature rupture of membranes), the high parity (vi), and the previous abnormal smears. No tumor was found on pathologic examination. This patient had 2 suspicious smears and a biopsy diagnosis of chronic cervicitis. In retrospect we believe that conization could have been deferred and the patient followed with further smears since she did not evidence any definitely positive smears. It seems likely that the cervical dystocia is related to the conization and should be considered as one of the possible complications of the procedure.

Comment

Based on our experience and the evidence presented by other investigators, we must support the view that atypical epithelial changes in the cervix during pregnancy are not transient and bear the same significance as those occurring in gynecologic patients.

With the possible coexistence of basal cell hyperplasia or carcinoma in situ with actual invasive carcinoma of the cervix, we believe that conization of the cervix must be utilized if we are to diagnose early invasive lesions during pregnancy. We also believe that this conization should be equally as extensive as in the nonpregnant patient, if we are to either exclude or establish the diagnosis of invasion.

This present series of diagnostic conizations of the cervix during pregnancy is admittedly quite small, and no final conclusions as to its merits or hazards can be drawn as yet. Additional experience may indicate that the number of serious complications from conization does not justify its use during pregnancy except in a limited number of cases. To date there does not seem to be a great enough hazard, in comparison to the possible benefits derived, to cause us to forego this diagnostic tool, and we shall continue to employ it in our routine. We believe the 1 patient in whom the diagnosis of early invasion was obtained may owe her life to the conization procedure.

Summary

1. The results of a preliminary study of the use of diagnostic conization of the cervix during pregnancy are presented. There were 2 abortions and 1 case of cervical dystocia possibly related to the procedure in 16 conizations.

2. No final conclusions, from this small series, can be drawn, but the benefits derived seem to overbalance the possible hazards of conization in pregnancy.

3. A plan of management of the pregnant patient involving routine cytologic screening, indicated biopsy, and full cold knife conization is suggested.

4. A yield of 1 invasive carcinoma in 16 pregnant patients subjected to conization is sufficiently good to warrant continued use of this diagnostic method.

5. Expanded use of the procedure seems indicated to afford the pregnant patient every protection against invasive carcinoma of the cervix.

Addendum. The 3 remaining undelivered patients have now completed their pregnancies; all had uncomplicated full-term labor and vaginal delivery.

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Deciduosis of the cervix manifesting as antepartum hemorrhage and simulating carcinoma

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IT IS current practice, whenever possible, to apply the principles of expectant treatment to cases of antepartum hemorrhage. When the intervening period between the onset of bleeding and definitive treatment is of any duration, most workers advise exposure and inspection of the lower genital tract to exclude the remote but definite risk of leaving a malignant lesion untreated. In our view, despite the fact that information of value is rarely obtained, this step must never be omitted. We have invariably applied this policy at the Jubilee Maternity Hospital. A case is reported here of the detection of the unusual condition, deciduosis, which closely mimicked cervical carcinoma.

Case report

Mrs. S. J., aged 26, gravida ii, para i, was seen for antenatal care at the Maternity Department of the Belfast City Hospital during her second pregnancy. The only possibly significant fact noted from her previous history, in view of subsequent developments, was that she had received diathermy treatment for a cervical erosion following her first delivery at another hospital. During her first pregnancy and labor no abnormality had been observed.

The first 36 weeks of her second pregnancy passed without incident. On April 4, 1959, she came to the Department for a routine visit and reported two episodes of slight painless fresh vaginal bleeding during the preceding week. She had not thought it fitting to seek medical aid in view of the scanty and transient nature of the bleeding. The absence of any form of the toxemia of pregnancy coupled with an unengaged presenting part prompted the tentative diagnosis for a minor degree of placenta previa. She was admitted for investigation and appropriate treatment. On admission her clinical condition was good and, in accordance with the practice of the Unit, a speculum examination was done to exclude any abnormality of the lower genital tract. This revealed a mass of polypoid, bright red, granuloma-like tissue on the anterior vaginal wall which appeared to surround and cover the cervix (Fig. 1). Clinically, the condition resembled a carcinoma, though its consistency seemed perhaps too "velvety." A portion of the proliferation was removed for biopsy and the fact that the tissue seemed suspiciously friable was noted. An urgent histological report was requested and read: "The material submitted shows a decidual reaction. Large cells with abundant cytoplasm are present and are lying deep to a squamous epithelium. In a few areas the squamous epithelium is ulcerated and there is some granulation tissue present. It is possible that very prolonged search might reveal some glandular elements, but none have been found and are not necessarily a part of the condition. The condition is designated deciduosis and is defined as a transformation of connective tissue, other than endometrial stroma, into decidual like cells." (Fig. 2.)

It was considered necessary, despite the above findings, to examine the patient while she was under anesthesia to exclude coexistent placenta previa as the head of the fetus remained above

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the pelvic brim. This was undertaken at the thirty-eighth week of pregnancy and revealed no evidence of low-lying placental tissue. The cervical and vaginal condition was unchanged in appearance. The patient was temporarily dismissed from the hospital and was seen twice at the antenatal clinic prior to the onset of labor 2 days past term. Labor progressed rapidly and normally to the spontaneous delivery of a living male infant in good condition who weighed 7 pounds, 2 ounces. At no stage was any untoward bleeding noted.

Inspection of the lower genital tract after delivery revealed considerable diminution in the decidual reaction and no bleeding or traumatized areas. The puerperium was uneventful and the mother and baby left the hospital on the seventh postpartum day.

The patient reported for postnatal examination 6 weeks after delivery, at which time pelvic examination showed almost complete disappearance of the condition described. This can be seen by comparing Fig. 3 with Fig. 1.

Comment

Deciduosis of the vagina and cervix in pregnancy is a rare condition and references to its occurrence are scant in the literature. Yet one finds that, when a deliberate search for decidual reaction is made, it is found to be present in 20 per cent of the cervical biopsy specimens examined in pregnancy.[4] McGee and Slate[4] observed 27 cases of frank deciduosis and mentioned the difficulty in making a clinical distinction from carcinoma, as was the case in the instance described above. This difficulty is also alluded to by

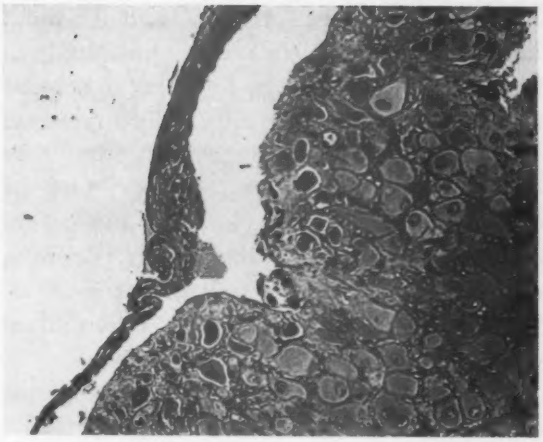

Fig. 2. Microscopic appearances of deciduosis.

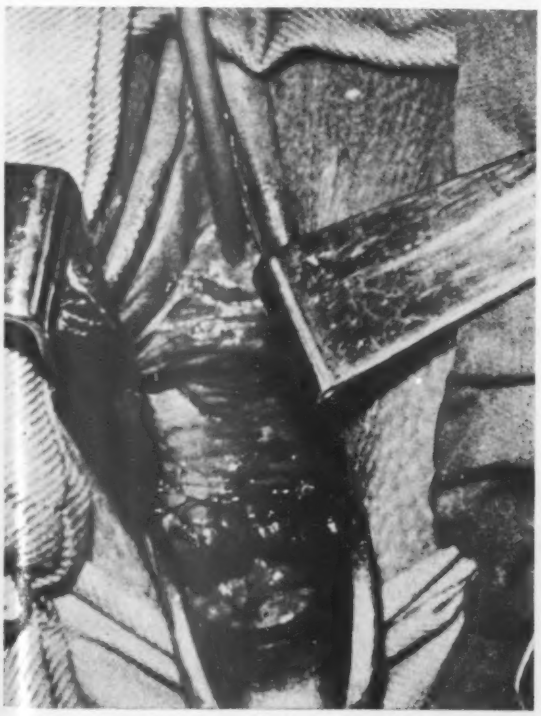

Fig. 1. Gross appearances of decidual reaction affecting the cervix and vagina.

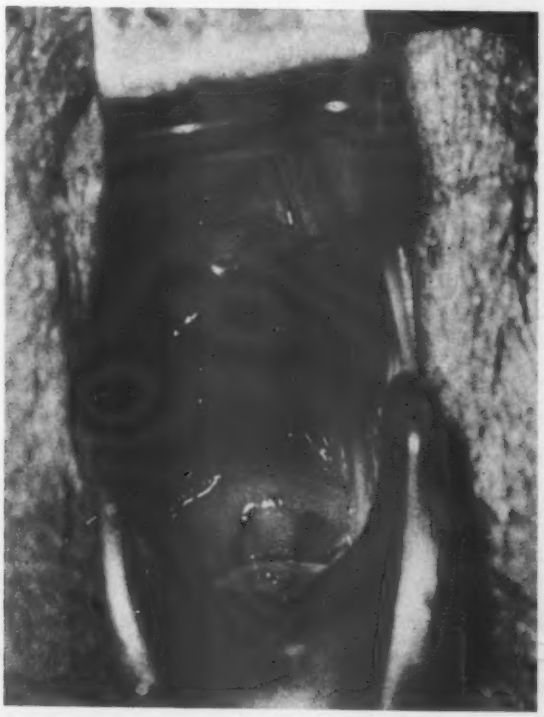

Fig. 3. Cervix and vagina 6 weeks post partum.

Klein and Luverne,[1] Lapan,[2] and Teleman and Teleman.[6] Klein's case presented as antepartum hemorrhage and was diagnosed clinically as a carcinoma. This impression was corrected after biopsy. Bleeding occurred at biopsy only *after* labor. One of Lapan's 3 patients was, in fact, told before coming to him that she had cancer. Teleman and Teleman also point out the necessity of histological examination to differentiate deciduosis from cervical malignancy.

The etiology of the condition is obscure although McGee[4] states that, presumably, the explanation lies in a response of stromal cells of mesenchymal origin to the hormones of pregnancy. Lervin[3] is quoted as finding decidua in 36.5 per cent of cervical polyps examined in pregnancy and cites inflammation as a cause. We tentatively suggest that the decidual reaction might possibly have arisen in endometrial elements implanted in the patient's cervix at the time of the previous curettage and diathermy treatment. It seems plausible, despite the absence of glandular elements in this case, that implantation of endometrium could well occur during such a procedure. We are gratified to note that Novak and Novak,[5] hitherto opposed to implantation theories in the etiology of endometriosis, favorably quote Dr. Louise Branscombe who described 14 definite cases of surface endometriosis of the cervix, all following cauterization procedures. We hope, in the near future, to undertake a study to confirm this work and perhaps trace any detected implants throughout pregnancy. We believe that a study such as this might help to clarify in some measure the current difficulties experienced by clinician and pathologist alike in interpreting the often bizarre and confused gross and microscopic changes found in the cervix during pregnancy.

Summary

1. The case for routine inspection of the cervix and vagina during the observation of bleeding at all stages of pregnancy is reemphasized.

2. A case of deciduosis of the cervix and vagina presenting as antepartum hemorrhage is described. The rapid return to normal of the lower genital tract in the puerperium is illustrated.

We wish to thank W. S. Campbell, Esq., F.R.C.S., F.R.C.O.G., into whose ward the patient was admitted, for permission to publish this material, and J. Edgar Morison, Esq., M.D., D.Sc., consultant histopathologist, for his invaluable help on this and other occasions.

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GYNECOLOGY

Cervical leukoplakia

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LEUKOPLAKIA of the cervix is a precancerous lesion just as it is on other mucosal surfaces. Our recently acquired knowledge of carcinoma in situ has done much to establish this fact. Yet, in many of the major gynecological texts of today, cervical leukoplakia is barely mentioned, and then only as a gross finding with no relation to cancer.[1-6] This report adds more evidence of the association of leukoplakia with cervical carcinoma.

Materials

The material providing the basis for this paper consists of 23 cases of leukoplakia of the cervix. All were studied histologically. In 9 cases, the entire cervix was available for pathologic examination, in 8 cases a cold-knife cone biopsy was studied, and in 7 smaller biopsies of varying sizes were submitted. Because, in many cases, cone biopsies preceded hysterectomy, a total of 36 cervical tissue specimens were examined. These were among a total of 1,722 cervical specimens examined over the same period of time. Cervical smears were available from 15 of the 23 patients studied. Thirteen cases of leukoplakia were first observed clinically in the private practice of one of us (P. H. H., Jr.). These were found during the course of 12,085 vaginal examinations from 1953 to 1960. In this same period of time, 18 patients with carcinoma in situ were seen. Many were referred by other physicians after suspicious or positive Papanicolaou smears were found. Among these patients, 6, or 33 per cent, had gross leukoplakia.

The average age of the group of 23 patients was 41 years. Those with invasive carcinoma averaged 53 years; with carcinoma in situ, 42 years; and with leukoplakia without malignancy, 31 years.

Methods

All biopsies, including cone biopsies, were cut into 2 to 3 mm. slices and processed for histologic study. When the entire cervix was available, it was processed by the procedure described by Foote and Stewart, modified so that the tissue slices were not sectioned individually.[7] All sections were stained with hematoxylin and eosin. The term "carcinoma in situ" is used as delineated by Reagan and Hamonic.[8] Three pathologists reviewed the 12 cases of carcinoma in situ. All agreed without reservation that carcinoma was present in each case, but, in several cases, one or two pathologists suggested the possibility of microinvasion.

For the microscopic diagnosis of leuko-

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plakia to be made, 4 features were required. These criteria, which were present in every case, included epithelial hypertrophy with acanthosis, hyperkeratosis, a stratum granulosum, and a lymphocytic infiltration of the superficial stroma.[9, 10]

Cervical smears were stained with Papanicolaou stain and were evaluated for the presence of anucleate squames and cells containing keratohyalin granules as well as dysplastic and malignant cells.

Case reports

The following 3 representative cases of leukoplakia of the cervix are presented to illustrate the symptoms, clinical findings, and management.

Case 1. Mrs. B. C., aged 34, gravida iv, para iii, with 1 abortion, was first seen on Jan. 31, 1958, with the complaints of heavy leukorrhea and occasional spotting between periods. Examination revealed an area of leukoplakia on the anterior lip of the cervix and chronic cystic cervicitis. The area of leukoplakia was elevated and could not be removed by sponging. Wet smear revealed *Trichomonas vaginalis*. Papanicolaou smears were negative except for a few anucleate squames. The serologic test for syphilis was negative. The patient was treated with vaginal suppositories and vinegar douches for 3 weeks. The leukoplakia persisted and she was admitted to the hospital. The cervix was painted with Schiller's iodine solution. Only the leukoplakic area failed to take the iodine stain. With the patient under general anesthesia, a cone of the cervix was obtained with a scalpel. In this case a wide cone was necessary to treat the chronic cystic cervicitis. Sutures of 0 chromic were placed at 3, 6, 9, and 12 o'clock for hemostasis. The pathological findings were those of chronic cervicitis and cervical leukoplakia without dysplasia. Examination 5 weeks later disclosed that the cervix was healed.

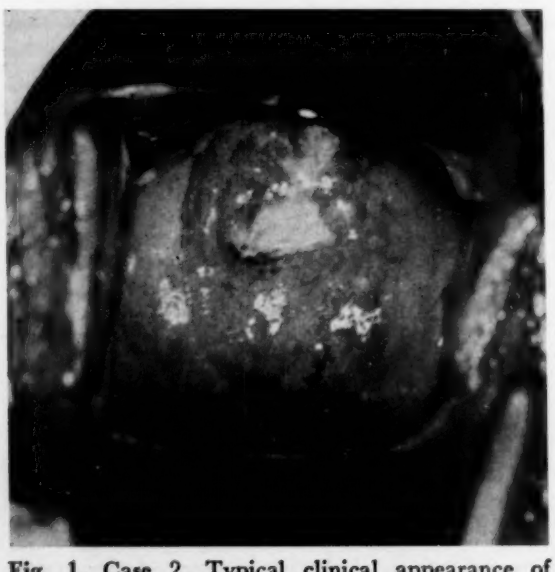

Fig. 1. Case 2. Typical clinical appearance of cervical leukoplakia. Note extension of leukoplakia into cervical canal where carcinoma was found.

In October, 1958, and again in January, 1960, recurrent leukoplakia was excised with a scalpel. Both recurrences occurred at the site of the original lesion. The cervix healed completely after each excision. Papanicolaou smears have been consistently negative for dysplastic or malignant cells and histologic study of the excised tissue has revealed leukoplakia without dysplasia. Periodic examinations at 6 month intervals have been scheduled.

Case 2. Mrs. A. R., aged 50, gravida 0, para 0, was referred by an internist on Dec. 26, 1959, with the complaints of bloodless leukorrhea for 2 months and a suspicious Papanicolaou smear, Class III. On examination of the cervix (Fig. 1) there was an extensive, irregular, elevated, whitish area involving the anterior lip of the cervix and extending into the cervical canal. When the cervix was painted with Schiller's iodine solution there was a band of tissue adjacent to the leukoplakia that did not take the stain. The serologic test for syphilis was negative. The patient was admitted to the hospital on Dec. 31, 1959, and superficial conization of the cervix and curettage were done. Pathological reports showed leukoplakia with marked dysplasia and adjacent carcinoma in situ (Fig. 2). One area showed possible microinvasion. Clinically, the carcinoma was in Stage 0. On Jan. 2, 1960, a Wertheim hysterectomy without node dissection was performed. Adequate vaginal cuff was insured by vaginal incision of the vaginal mucosa just prior to hysterectomy. The pathological report revealed carcinoma with microinvasion still present high in the endocervical canal.

Case 3. Mrs. D. S., aged 45, gravida vi, para v, had had 1 abortion. She was first seen Sept. 10, 1957, with the complaints of intermenstrual vaginal bleeding, especially postcoital, for 1½ years. Examination showed an irregular, friable,

ulcerated area about the entire cervical os. There were whitish gray patchy areas about the edges of the lesion. In the endocervical canal there was a large ulcerated cavity. The tumor extended for several centimeters into the left parametria, and a firm nodular area was palpable on the left lateral pelvic wall in the region of the iliac artery bifurcation. Papanicolaou smears were positive (Class V). The serologic test for syphilis was negative. The patient was admitted to the hospital and multiple punch biopsy specimens were taken from the lesion. Measurements for later radium insertions were made. Schiller's iodine revealed a wide area of tumor and leukoplakia that did not stain. Conization was not done. Pathological study revealed invasive epidermoid carcinoma (Grade III) and leukoplakia with marked dysplasia. X-rays of the chest and pelvis were negative. Intravenous pyelograms were normal. The patient was treated with radium and x-ray therapy by the Manchester technique. She was last seen in March, 1960, when there was no evidence of recurrence.

Findings

Experience with these cases indicates that cervical leukoplakia which fulfills the histologic criteria for this diagnosis has a relatively typical, easily recognized gross appearance. It presents as a whitish area against the pink background of the cervical mucosa. The degree of whitish discoloration varies but does not escape detection when the examiner is looking for it. The extent of involvement varies widely, from small patches only a millimeter or less in diameter, to instances in which the entire ectocervix is involved. The irregular margins, though usually sharp, may be poorly defined. In some instances the surface is relatively smooth while in other cases it is rough or irregular. These areas of whitish discoloration usually do not scrape off with a tongue blade, but, when they do, a roughened, reddish, sometimes bleeding surface is left. Involved sites do not stain with Schiller's iodine.

Other lesions that may be confused with leukoplakia are usually easily recognized. The pallor over a tense Nabothian cyst and the fluffy cheezy exudate of moniliasis, which scrapes off readily, should cause no confusion. A blood test aids in excluding syphilitic leukoplakia. Cervical pachydermia associated with uterine prolapse is recognized by the diffuse, leathery thickening of the mucosa, which often has a yellowish cast, and by the history of chronic procidentia uteri with substantiating physical findings. The dark gray or gray-brown membrane of pseudomembranous cervicitis is usually easily identified.

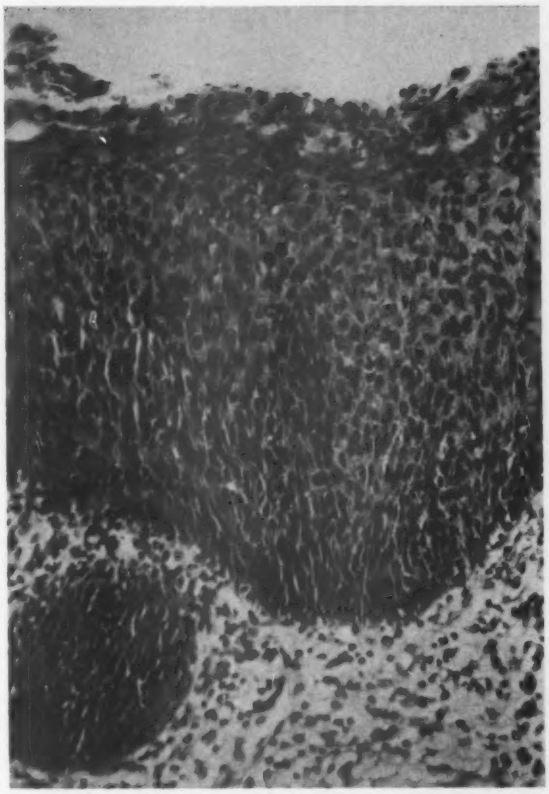

Fig. 2. Carcinoma in situ, from the same case as illustrated in Fig. 1. (×275; reduced ⅓.)

The histologic features of cervical leukoplakia are identical to those of leukoplakia of the vulva or any other site (Fig. 3). There is a wide variation in degree of hyperkeratosis and acanthosis not only from case to case but also in different areas of the same specimen. One area may have a smooth surface while another area exhibits such marked papillation as to justify a diagnosis of papilloma (Fig. 4). In the same manner, one section may disclose no dyskeratosis and another section may exhibit marked dyskeratosis. Parakeratosis is likewise variable

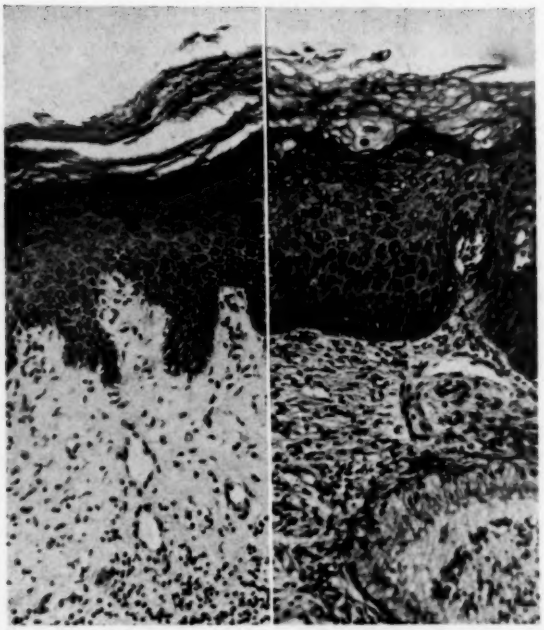

Fig. 3. This composite photomicrograph demonstrates the histologic features of leukoplakia of the vulva (left) and cervix (right). Note the similarity of the epithelial changes. Elsewhere the cervix was the site of carcinoma in situ. (×150; reduced 4/5.)

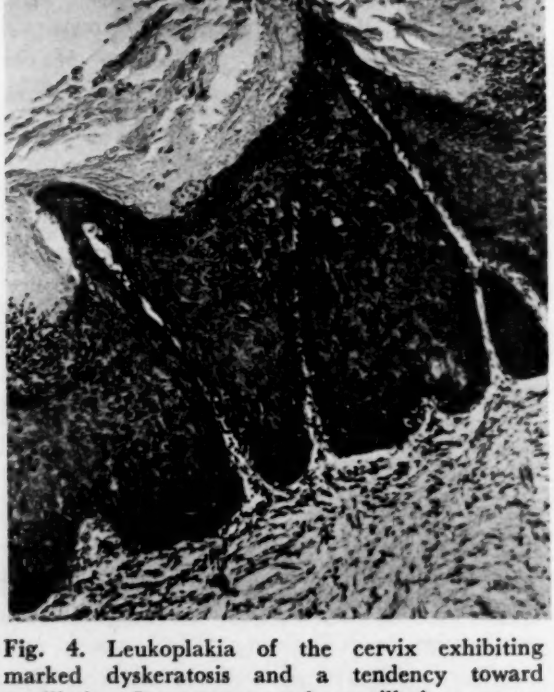

Fig. 4. Leukoplakia of the cervix exhibiting marked dyskeratosis and a tendency toward papillation. In many areas the papillation was not present and at other sites it was more pronounced. (×150; reduced 3/8.)

but becomes more prominent in areas of most marked dyskeratosis. As would be expected, the stratum granulosum tends to be best developed where hyperkeratosis is most striking.

The 23 cases of leukoplakia exhibited the following coexisting changes: carcinoma in situ, 12; invasive squamous cell carcinoma, 4; no dyskeratosis, 4; noncarcinomatous dyskeratosis, 3.

The 4 cases without dyskeratosis were all studied clinically and were grossly typical of cervical leukoplakia. Case of so-called pachydermia due to uterine prolapse and syphilis were excluded. In 2 of these 4 cases leukoplakia recurred after complete excision. Of the total group, 16 of 23 (69 per cent) were associated with malignancy. In 6 cases transitions from leukoplakia to carcinoma in situ or invasive carcinoma could be demonstrated in the same section in a continuous segment of epithelium. The 12 instances of carcinoma in situ were included among a total of 52 cases so diagnosed pathologically during the same period of time. Thus, 23 per cent of cervices showing carcinoma in situ also presented leukoplakia histologically. Among the 13 cases of leukoplakia observed clinically, 6 had coexisting carcinoma in situ, 5 had no malignancy, and 2 had invasive carcinoma. Thus, of the cases seen clinically in the practice of gynecology, 61 per cent were associated with malignancy.

Study of the cervical smears confirmed the findings reported elsewhere in the literature.[8] Anucleate squames in varying numbers were always present though sometimes sparsely scattered. Cells containing keratohyalin granules were less frequently found and dysplastic or malignant cells closely correlated with the subsequent histologic sections. In several instances it was possible to make a cytologic diagnosis of leukoplakia without prior knowledge of the gross appearance of the cervix.

Management

Clinically typical leukoplakia should be confirmed by histologic study and Papanicolaou smears should be examined. Caution is

necessary to avoid a cone biopsy through invasive carcinoma. Ulcerated, friable, or exophytic lesions should be studied by punch biopsy. When leukoplakia is confirmed and there is no evidence of invasive carcinoma, further study is necessary to exclude early coexisting malignancy. Such patients are admitted to the hospital. In the operating room, under general anesthesia, the patient is prepared for conization. The entire cervix is painted with Schiller's iodine solution.[11] Then a superficial cone of cervical tissue, including all areas giving a negative reaction for glycogen, is removed with a scalpel. Sturmdorf stitches of No. 0 chromic catgut are placed at 3, 6, 9, and 12 o'clock to help minimize the otherwise troublesome bleeding that can occur with this procedure.

When carcinoma in situ is found, a total hysterectomy is done with removal of a wide vaginal cuff. Just prior to operation the cervix is painted with iodine. The vaginal mucosa is then incised about the area which fails to stain. This procedure is followed to insure adequate cuff excision and to reduce the chance of recurrent carcinoma to an absolute minimum (Fig. 5).

If the leukoplakia is not associated with malignancy, the patients are asked to report every 6 months for Papanicolaou smears and vaginal examination. In essence, cervical leukoplakia is managed the same as vulvar leukoplakia. Leukoplakia alone has not been considered an indication for hysterectomy.

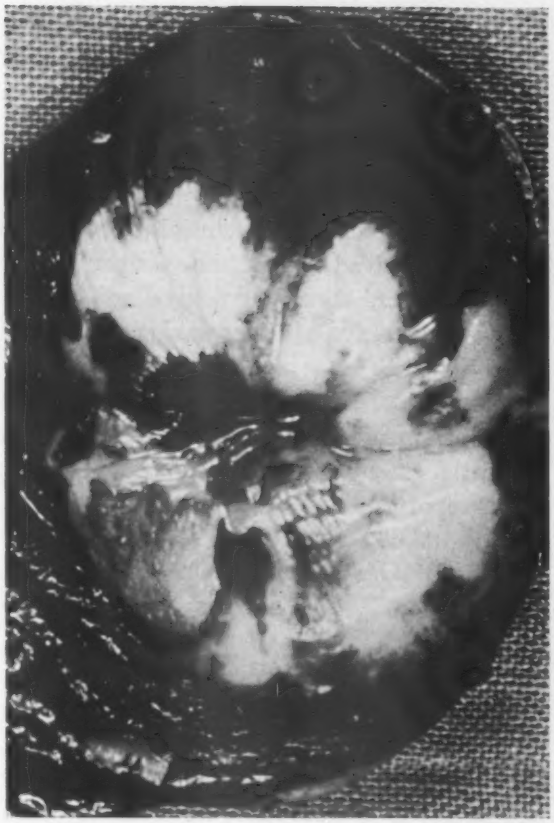

Fig. 5. Surgical specimen from case of typical leukoplakia of cervix after Schiller's test. Adjacent wide, nonstaining areas histologically revealed dysplasia and carcinoma in situ.

Comment

In 1930, Hinselmann published a thorough study with microscopic classification of cervical leukoplakia and indicated that it was a premalignant lesion.[12] Shortly thereafter a fellow countryman, Robert Meyer, stated that leukoplakia was merely a white patch on the cervix and not important in the development of cervical cancer.[13-15] He also disagreed with some of the microscopic diagnoses in Hinselmann's series. This is understandable, since at that time there was little knowledge of carcinoma in situ. Many writers of gynecologic textbooks have followed Dr. Meyer's assumption. Dr. Karl Martzloff's excellent paper of 1932 stressing the premalignant nature of cervical leukoplakia has apparently been overlooked.[16] If one examines the findings of Drs. Hofmeister and Gorthey, misunderstanding regarding cervical leukoplakia is even more apparent.[17] In 1955, they sent questionnaires to 434 specialists in obstetrics and gynecology and found that only 50 per cent considered leukoplakia of the cervix to be precancerous and over 25 per cent would not even bother to biopsy a leukoplakic area on the cervix. Further review of the literature reveals that several authors have reported a high incidence of leukoplakia in cervices involved by carcinoma in situ. Wespi[18] found this association in 25 per cent of his cases of carcinoma in situ; Lang,[19] in 30 per cent; and Dockerty,[20] in 10 per cent. These figures are consistent with our finding of 23 per cent.

The cytopathologic studies of Reagan and Hamonic are interesting in this regard since these writers found evidence of hyperkeratosis in cervical smears in 18 of 100 cases of in situ cancer.[8] In some instances these were "associated with polygonal cells containing granular cytoplasmic inclusions that are probably derived from the deeper lying granular layer." Such cytologic findings are strongly suggestive of leukoplakia.

In sharp contrast to this high incidence of leukoplakia in patients with carcinoma in situ, the incidence of leukoplakia in the general female population is extremely low. Baker reports 14 cases of cervical leukoplakia among 103,685 gynecologic hospital admissions.[21] Of this group, 8,906 had cervical cauterization. On this basis there was an incidence of less than 0.013 per cent among the admissions to the gynecology service, and less than 0.16 per cent among patients treated with cervical cautery. In the series reported here there were 13 cases discovered during 12,085 pelvic examinations on obstetric and gynecologic patients, or an incidence of approximately 0.11 per cent.

The term "precancerous," as used in this discussion, indicates that the cervices which are involved by leukoplakia are predisposed to cancer. In this sense, patients presenting this lesion will have a significantly greater incidence of carcinoma of the cervix than women who do not have leukoplakia. It is not intended to imply that all cases of leukoplakia will inevitably develop cancer, nor is it suggested that the carcinoma will necessarily develop at the exact site of the leukoplakia, although this occurs.

The development of a stratum granulosum and hyperkeratosis as seen in leukoplakia indicates some degree of maturation or differentiation of the superficial epithelial cells. Carcinoma in situ, by definition, must present only undifferentiated cells in the full thickness of the epithelium.[8] Thus, although leukoplakia may present very marked dysplasia or dyskeratosis, the diagnosis of carcinoma in situ in this study has been based on changes in the cervical epithelium adjacent to or even completely removed from the leukoplakic areas. In studying these specimens, one often finds a gradual transition from leukoplakia with varying dyskeratosis, to areas of marked dysplasia more often with parakeratotic surface cells, to unequivocal carcinoma in situ or invasive carcinoma. The clinical implications of this are at once apparent since a punch biopsy from the grossly typical leukoplakia may completely miss the malignant changes. The study of cervical smears becomes an important adjunct, but definitive evaluation depends on more extensive study than either of these procedures affords.

To complete this discussion the following points are given in support of the view that leukoplakia of the cervix is precancerous. First, the incidence of leukoplakia in patients with carcinoma in situ of 10 to 30 per cent is many times greater than the incidence of leukoplakia in a random selection of gynecologic patients where even the most liberal data indicate an incidence of less than 0.2 per cent. This difference would be even greater if one excluded patients with cervical carcinoma from the reference group. This relatively high incidence of leukoplakia in those patients with carcinoma in situ clearly indicates a highly significant relationship. Second, the histologic transition from leukoplakia to carcinoma in situ or invasive carcinoma in one section and in a continuous segment of epithelium, as observed in 6 of 15 cases of carcinoma in this series, further supports this relationship.

Having established that a relationship exists between leukoplakia and carcinoma, the time factor must be evaluated. Obviously, leukoplakia must precede the associated malignancy if it is to be regarded as a *pre*cancerous lesion. The strongest evidence in this regard is the fact that cases have been reported of patients with cervical leukoplakia who, with a lapse of time, developed carcinoma while under a physician's care.[21-28] The total number of such cases is small, however. Second, at other sites where leukoplakia and carcinoma have a significant relationship of coincidence, leukoplakia has been clearly established and almost univer-

sally accepted as *pre*cancerous. In this regard, the histologic identity of cervical leukoplakia with that of other areas assumes importance. Finally, the average ages of the patients herein reported with leukoplakia without carcinoma (31 years) as contrasted to those with coexisting carcinoma in situ (42 years) and invasive carcinoma (53 years) is certainly consistent with a precancerous relationship.

Conclusions

With experience, cervical leukoplakia is usually easily identified clinically. However, it should be confirmed by pathologic study applying the same histologic criteria used to diagnose this lesion on the vulva or any mucosal surface. When diagnosed in this manner, cervical leukoplakia has the same significance as leukoplakia of any other site. Our findings suggest that from the first appearance of leukoplakia it may take 10 years or more for carcinoma in situ to appear and 20 or more years for invasive cancer to supervene. Failure to appreciate the magnitude of this time factor and the earlier lack of knowledge of the significance of carcinoma in situ has hindered recognition of leukoplakia of the cervix as a precancerous lesion.

Summary

1. Twenty-three cases of cervical leukoplakia are reported. In 69 per cent of these cases there was coexisting carcinoma in situ or invasive carcinoma.

2. Leukoplakia of the cervix is reviewed and the evidence for its precancerous significance is presented.

3. Clinical and microscopic criteria for the diagnosis of cervical leukoplakia are stressed.

4. The management of patients with cervical leukoplakia is outlined.

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Leukoplakia of the cervix—the mosaic and papillary pattern

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AS EARLY as 1933, Hinselmann[1] and other German gynecologists were mentioning mosaic leukoplakia, papillary leukoplakia, and the mosaic pattern of the cervix. However, in speaking of leukoplakia, American gynecologists generally refer to a different type—a white patch on the cervix. This white-patch leukoplakia, which consists mainly of hyperkeratinized squamous epithelium and is considered rather harmless, has been seen only rarely at the White Memorial Clinic of the College of Medical Evangelists. The mosaic-pattern leukoplakia never had been clinically diagnosed at our Gynecology Clinic before 1957.

A vital current need is for a universal, specific definition of the term "leukoplakia." The necessity of such a definition has been emphasized during the year September, 1958, to September, 1959, in the Gynecology Clinic where, using the combined approach (routine Papanicolaou and indicated colposcopic examination) we have diagnosed only occasionally the so-called white-patch leukoplakia, but we have observed 51 cervices with mosaic-pattern leukoplakia.

This mosaic pattern is not a patch *on* the epithelium; it comprises *the epithelium itself*. Because it has been overlooked almost completely in the tumor clinics of the White Memorial Hospital until the past 2 years, it seems probable that throughout the United States this condition is more often overlooked than diagnosed.

To the naked eye the cervix may appear normal, yet under colposcopic lens magnification accentuated by application of the Hinselmann test (3 per cent acetic acid), the mosaic or papillary pattern usually develops in a clearly delineated frosty gray pattern.

By cross-checking with the Schiller test (iodine 10 Gm., potassium iodide 30 Gm., and distilled water q.s. ad 500 c.c.) the affected areas are sharply bordered yellow noniodine staining, whereas the normal mucosa stains dark mahogany brown. In all of the cases which we have observed, where a definite mosaic pattern existed, it has been irreversible. Even after as long as 6 months of antiseptic and hormone treatment, exactly the same pattern persisted. The only exceptions have been a few cases where the entire area was biopsied—so the lesion had probably been totally removed.

It is true that this mosaic or papillary appearance may be present occasionally when the biopsy is negative. On the other hand, almost 100 per cent of our in situ carcinomas (about 40 in number) have been associated with this mosaic or papillary pattern. Almost all of our cases of premalignant dyskeratosis and basal atypical hyperplasia (about the same number as in situ carcinoma) are also associated with this pattern.

We also feel that this pattern when associated with pregnancy is not usually a reversible change caused by the pregnancy. Three

From the Department of Obstetrics and Gynecology of the College of Medical Evangelists.

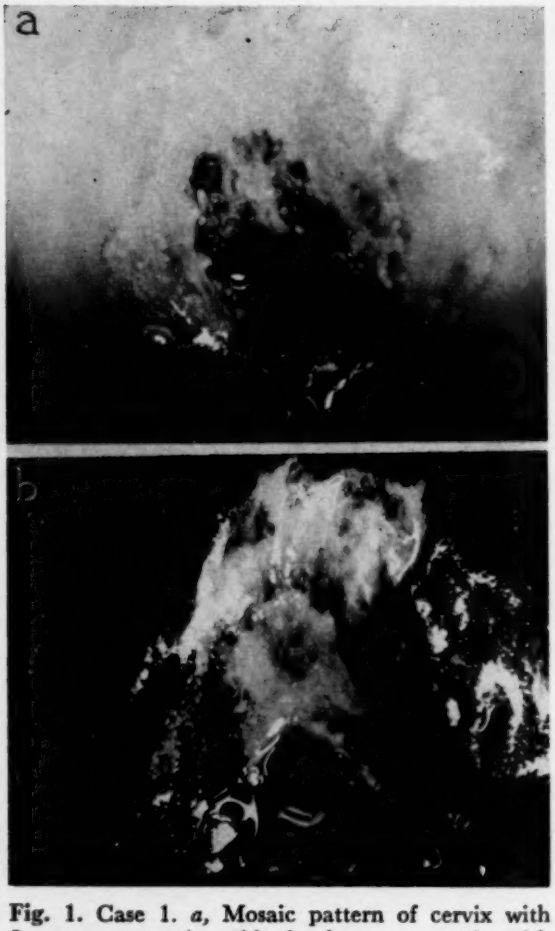

Fig. 1. Case 1. *a*, Mosaic pattern of cervix with 3 per cent acetic acid; *b*, the same cervix with Schiller's stain.

pregnant patients have been followed until several months after delivery, and this same pattern was still persistent. One patient, 6 months pregnant, gravida iv, para iii, aged 33, had a Papanicolaou Class IV smear. Colposcopic examination revealed a wide area of mosaic and papillary pattern. Biopsy and conization showed early invasive carcinoma. The pregnancy was allowed to go to 38 weeks, a cesarean section performed, and x-ray and radium therapy instituted. Another patient, aged 33, gravida v, para iii, with one abortion, 5 months pregnant, showed an abnormal colposcopic pattern in the endocervix. Papanicolaou smear was Class III. She was followed 2 months post partum with the same grayish pattern, especially just around the external os. Repeat Papanicolaou smear was Class III, b. Four months post partum, the same picture persisted. A cold-knife conization was done with a diagnosis of carcinoma in situ. This was followed by a total hysterectomy with areas of residual premalignant dyskeratosis. Still another patient, aged 25, gravida ii, para i, 4 months pregnant, with a Class V Papanicolaou smear, showed this marked abnormal mosaic pattern under the colposcope. A careful cold-knife conization was done notwithstanding the pregnancy. The diagnosis was in situ carcinoma. She carried to term. Four months post partum there was only a small Schiller-yellow area. This was taken for tissue culture growth. The result was better than average growth and the cells did not appear normal. The patient is to return again for follow-up studies. Here we have an in situ lesion apparently adequately treated by conization; however, this cervix is still abnormally active in tissue culture growth. Should a hysterectomy be done in such a patient? These are the unanswerable questions in gynecology at present. Certainly close observation is necessary.

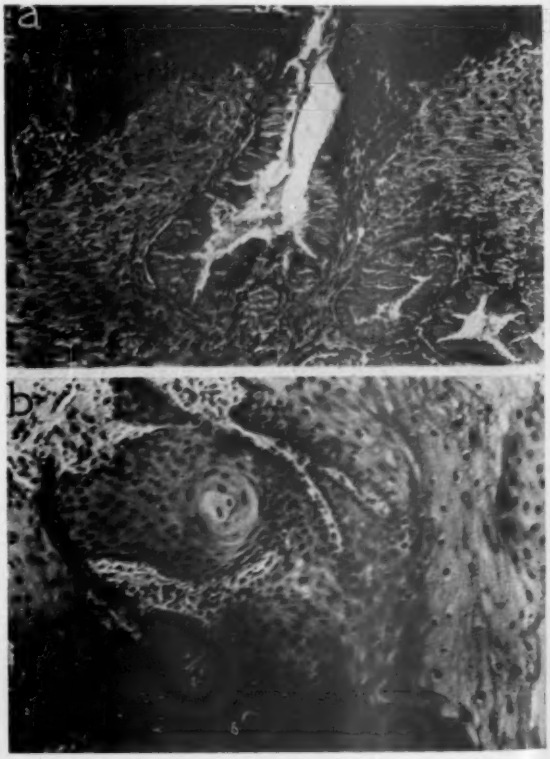

Fig. 2. Case 1. Microscopic sections showing atypical basal hyperplasia and premalignant dyskeratosis.

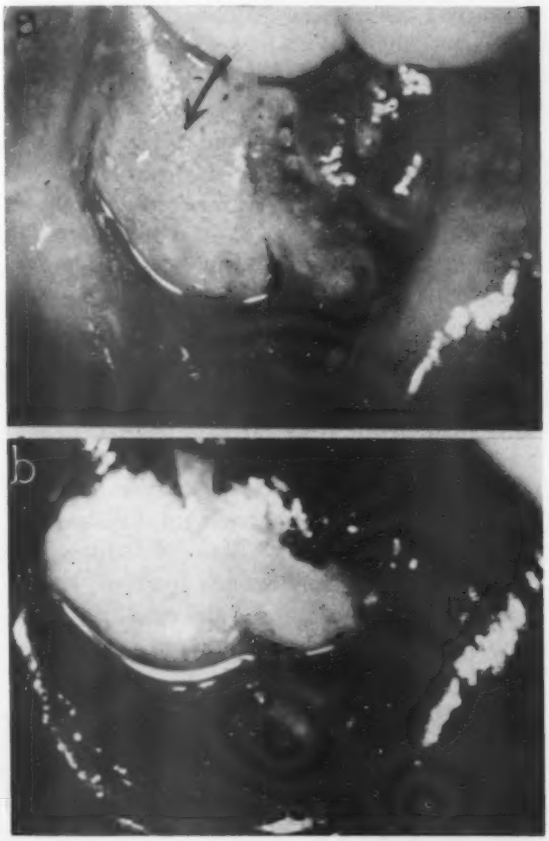

Fig. 3. Case 2. *a*, Mosaic pattern of endocervix with acetic acid; *b*, with Schiller's stain.

That this mosaic pattern is frequently premalignant probably can be assumed; it certainly is abnormal. While all of the early cancers of the cervix which we have observed were associated with this pattern, even some invasive and ulcerating malignancies have had a border of squamous epithelium with this mosaic pattern.

We have just begun to correlate tissue culture of the mosaic-pattern areas in an effort to determine the premalignancy or actual malignancy factor of these early lesions.

In the meantime, we suggest that the term "mosaic pattern" or "mosaic leukoplakia" of the cervix or "atypical cervix" should be used clinically to distinguish this condition from simple, white-patch leukoplakia of the cervix. Furthermore, we suggest that pathologists no longer use the ambiguous term "leukoplakia of the cervix," but replace it with a more descriptive term such as "premalignant dyskeratosis." Strictly speaking, even "white-patch leukoplakia" is not a pathological diagnosis, but only a clinically descriptive term for hyperkeratinization.

Case reports

Case 1. This 35-year-old nullipara was symptom-free, but had a Class III Papanicolaou smear. She was examined with the colposcope on Oct. 21, 1958. The cervix showed a marked mosaic pattern confirmed by Schiller's test which showed a sharp border between the abnormal and normal tissue (Fig. 1). The patient was re-examined on November 11; the same picture was present. Cold-knife conization was done November 11 with a pathological diagnosis of atypical basal hyperplasia and premalignant dyskeratosis (Fig. 2).

Case 2. The patient, a 30-year-old gravida v, para iv, had had one abortion. Her last pregnancy was in 1955. She was symptom-free, but had a Class V Papanicolaou smear. She was examined with the colposcope on Nov. 4, 1958. There was a marked mosaic pattern of the endocervix, which was confirmed with Schiller's test (Fig. 3). Cold-knife conization was done with a pathological diagnosis of carcinoma in situ (Fig. 4). (The mosaic pattern seems to be more serious if located near the endocervix.)

Case 3. The patient, aged 32, gravida ii, para ii, had her last pregnancy in 1950. She complained of spotting after intercourse. Papanicolaou smear was reported to be Class I. Colposcope examination Dec. 11, 1958, showed a mosaic pattern. One sister has the same mosaic pattern. Schiller's test confirmed a sharp-bordered

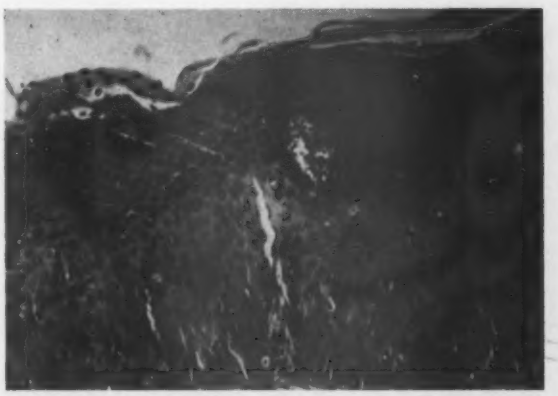

Fig. 4. Case 2. Microscopic sections showing in situ carcinoma.

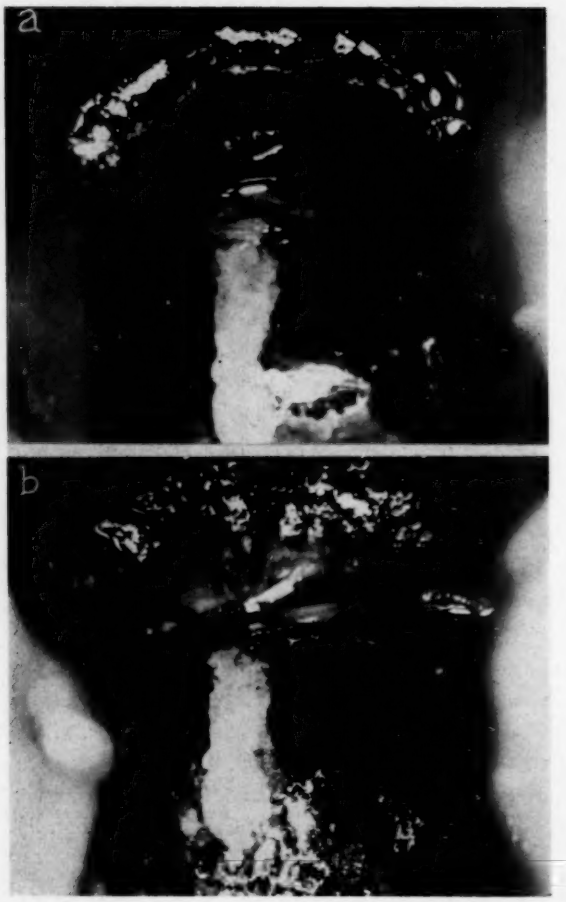

Fig. 5. Case 4. *a,* Mosaic pattern with Schiller's stain; *b,* the same pattern 3 months later.

abnormal area. Cold-knife conization was done with a pathological diagnosis of premalignant dyskeratosis and atypical basal hyperplasia.

Case 4. The patient, aged 58, gravida viii, para vi, with 2 abortions, went through the menopause at 42 years of age. Routine Papanicolaou smear was reported as Class III. She had had a previous subtotal hysterectomy. The cervix on colposcopic examination showed a slight mosaic pattern on the posterior lip. Schiller's test confirmed a sharp-bordered noniodine staining area (Fig. 5). She was treated for 3 months with antiseptic and hormone vaginal cream after which repeat examination showed the same picture. Biopsy diagnosis was chronic cervicitis with early atypical changes. The entire area was cauterized.

Case 5. The patient, aged 53, gravida iv, para ii, with 2 abortions, went through the menopause at the age of 48. Routine Papanicolaou test was reported as Class V. Colposcopic examination showed some irregular vascularity with a marked mosaic and papillary pattern of the entire left half of the cervix, especially posteriorly. This was confirmed by Schiller's test (Fig. 6). Biopsy diagnosis was early invasive carcinoma of the cervix, clinically early Stage I. It is now felt that if the predominant picture is a mosaic or papillary pattern, this represents in situ or very early invasive carcinoma, whereas if the pattern is predominantly a blotchy vascular one, this represents malignancy of a more advanced invasive nature.

Case 6. The patient, aged 33, gravida iv, para iii, with one abortion, had her last pregnancy 2 years previously. She was referred because of a cervical erosion. Papanicolaou smear was Class I. On colposcopic examination the area around the cervix was shown to be abnormal squamous tissue rather than the usual columnar tissue erosion. There was a marked mosaic pattern (Fig. 7). Because of the cytological findings, this patient is being followed with hor-

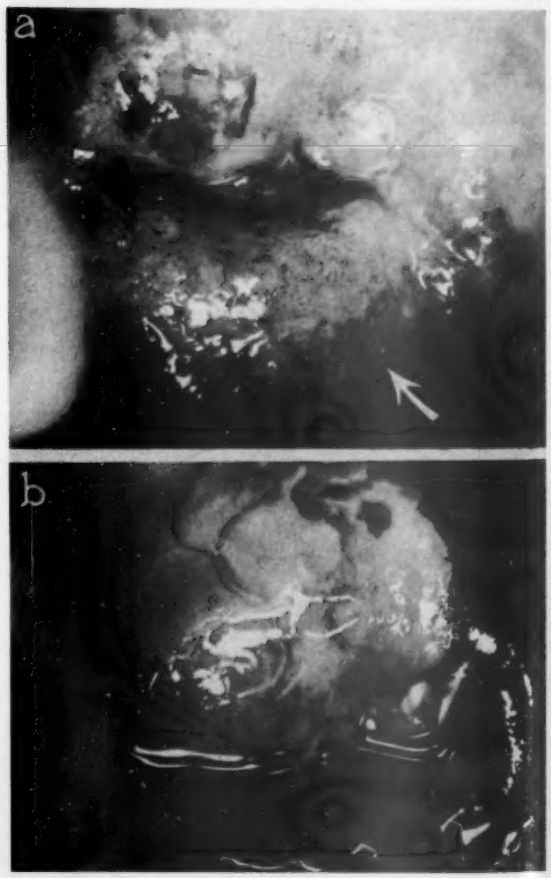

Fig. 6. Case 5. *a,* Marked mosaic pattern with early vascular irregularity; *b,* Schiller's stain showing sharp border between normal and abnormal areas.

mones and antiseptic vaginal cream. So far we have not seen this pattern reverse itself.

Case 7. The patient, aged 35, gravida vi, para vi, had her last pregnancy 6 years previously. She had some intermenstrual bleeding. Papanicolaou smear was Class III, b. On colposcopic examination there was a marked mosaic pattern, with Schiller's test showing a wide yellow abnormal area with a sharp brown border of normal mucosa (Fig. 8). Cold-knife conization confirmed the diagnosis of marked widespread carcinoma in situ in 13 of 16 slides. Because of the extensive area, a wide total hysterectomy (modified Wertheim) with a generous vaginal cuff was done. There was residual premalignant dyskeratosis but no node involvement.

Case 8. The patient was a 19-year-old gravida ii, para ii, Negro woman, who showed an abnormal Schiller yellow area. Papanicolaou smear was Class III, b. On colposcopic examination there was a wide transformation zone including

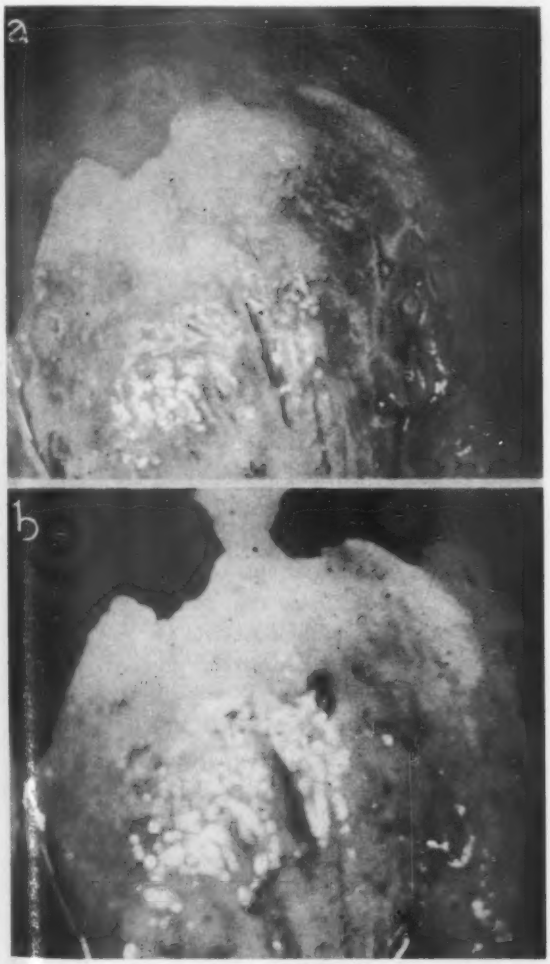

Fig. 7. Case 6. Mosaic pattern. *a*, With acetic acid; *b*, with Schiller's stain.

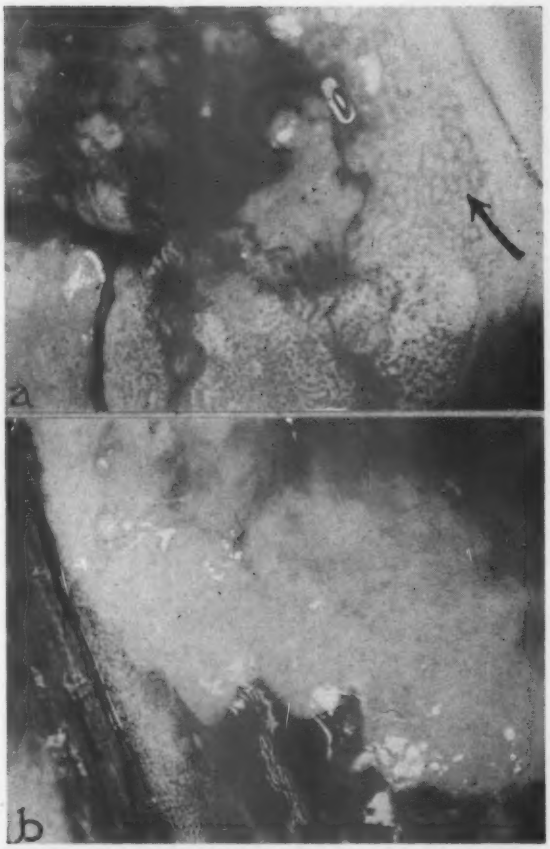

Fig. 8. Case 7. Marked widespread mosaic pattern. *a*, With acetic acid; *b*, with Schiller's stain. Diagnosis: widespread in situ carcinoma.

one area of a papillary grayish pattern (Fig. 9). With the Schiller test this area was yellow. It was biopsied with a diagnosis of carcinoma in situ. Tissue culture revealed a good growth even in the presence of Monilia. This also favors the diagnosis of malignancy. Because of the age of the patient, she is being followed closely after a cold-knife conization as a definitive curative procedure.

Case 9. The patient was a 29-year-old gravida v, para iv, with one abortion. Papanicolaou smear was Class III, b. On colposcopic examination there was a wide transformation zone surrounded by a definite mosaic pattern. Biopsy was done with a diagnosis of basal hyperplasia, premalignant dyskeratosis, and probably carcinoma in situ. Tissue culture showed only minimal growth. The patient has a sister, aged 30, gravida iii, para iii, with a Papanicolaou Class IV and in whom colposcopic examination showed a wide area of papillary grayish pattern around the os and extending anteriorly to the vaginal vault. This was in situ carcinoma.

Case 10. The patient was a 20-year-old

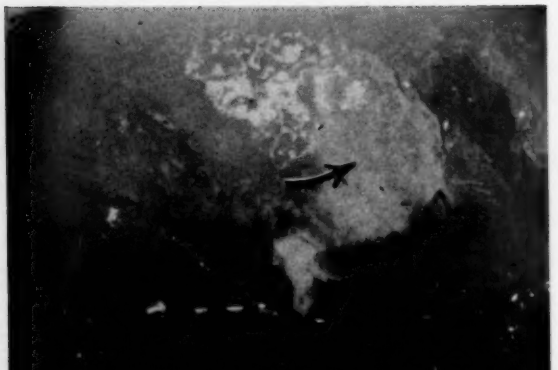

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Fig. 9. Case 8. Patient's age, 19. Biopsy of grayish papillary area (arrow) showing in situ carcinoma. *a*, With acetic acid; *b*, yellow with Schiller's test.

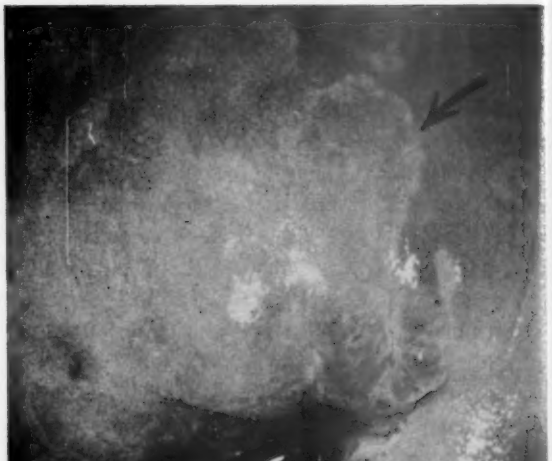

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Fig. 10. Case 10. Mosaic pattern. *a*, With acetic acid; *b*, with Schiller's stain.

gravida i, para i, referred in because of a Schiller yellow sharply bordered area. Colposcopic examination showed a marked mosaic pattern around the os (Fig. 10). Papanicolaou was Class I. A conization has been advised.

Case 11. The patient was a 22-year-old white woman, gravida ii, para ii, who had a total hysterectomy 6 months previously for widespread carcinoma in situ with one area of possible early tendency to invasion. After operation, the Papanicolaou smear persisted Class V after which review of the surgical slides showed the abnormal mucosal epithelium to extend to the excised margin. Colposcopic examination was done and this showed a papillary grayish pattern of the vaginal vault covering a 1 by 2 cm. area (Fig. 11). Excision biopsy of this area was done with a diagnosis of marked premalignant dyskeratosis, possibly in situ carcinoma. This case emphasizes the importance of staining the vaginal vault before doing the definitive procedure, and of making sure that the excision margin extends well beyond the sharp yellow and brown border.

Case 12. The patient was a 43-year-old gravida iii, para iii, whose last pregnancy was 9 years previously. She had a Class V Papanicolaou smear. The colposcope showed a very marked mosaic pattern around the external os, especially on the posterior lip. While the pattern was extremely marked, there was no abnormal vascular pattern (Fig. 12). The diagnosis from conization and hysterectomy was a widespread marked in situ carcinoma.

Summary

Of what significance is this grayish mucosal pattern, especially noted with the

application of acetic acid? It is at times papillary and at other times is a marked mosaic or cobblestone pattern. Usually there is a sharp border between the abnormal and normal areas. In our series of over 100 cases, a definite pattern of this type has not undergone spontaneous remission or, if associated with pregnancy, it has not disappeared after the pregnancy. The only ones that have disappeared are those that have been removed—small areas by biopsy, most of them by cold-knife conization. Hormone or antiseptic cream is of no value in effecting a change.

We have found this pattern by colposcope examination in 51 patients from September, 1958, to September, 1959. In these patients 21 cases were diagnosed on biopsy or conization as premalignant dyskeratosis, atypical basal hyperplasia or marked parakeratosis—all abnormal, but not malignant according to present-day pathological malignancy criteria. There were 19 cases of in situ carcinoma, 3 of in situ carcinoma with early invasion, and 6 of invasive cancer with a peripheral border showing the mosaic pattern —a total of 28 cancers associated with this pattern. In addition there were 9 more invasive cancers not showing any area of mosaic pattern but only the characteristic irregular blotchy vascular pattern.

And of course the great unanswered question still remains. Where does malignancy begin—hyperkeratosis, parakeratosis, atypical squamous metaplasia, premalignant dyskeratosis, basal hyperplasia, atypical basal hyperplasia, carcinoma in situ, or in situ with early invasion?

It is our opinion at the present time that almost always (except for occasional close observation) the mosaic or papillary pattern should have a cold-knife conization to a point well beyond the abnormal pattern. If the diagnosis is in the premalignant group according to present interpretation, this is probably sufficient, followed, of course, by close observation. If the diagnosis is carcinoma in situ, early invasive or invasive cancer, then further operation or radiation therapy is indicated.

Fig. 11. Case 11. Vaginal vault with Schiller's stain showing abnormal mucosa remaining after total hysterectomy.

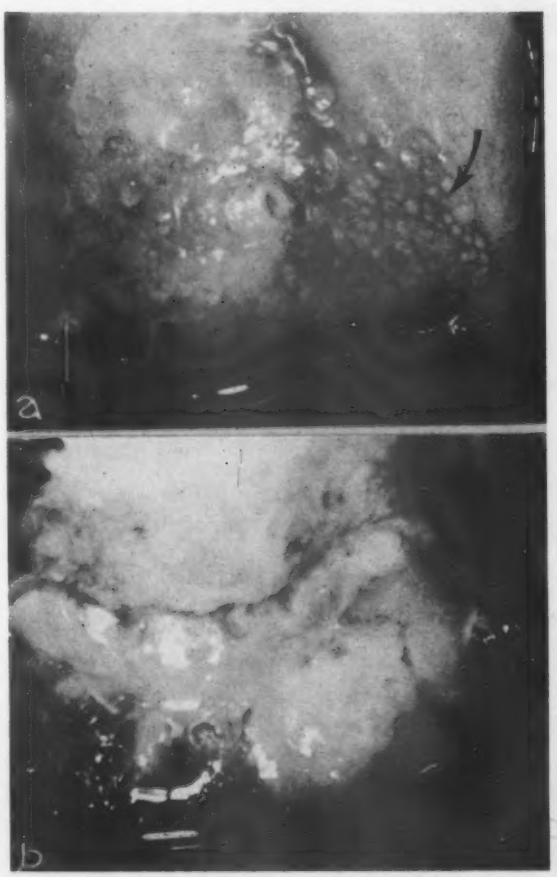

Fig. 12. Case 12. Widespread marked in situ carcinoma. *a*, With acetic acid; *b*, with Schiller's stain.

It is of interest that 10 patients with premalignant dyskeratosis had a Papanicolaou smear of Class I or II; 3 of those with in situ carcinomas and 4 with invasive carcinomas also had a Class I or II Papanicolaou smear. This is a total of 17 abnormal cervices where cytology screening would not have picked this up.

Conclusions

The mosaic and papillary pattern or mosaic and papillary leukoplakia of the cervix with acetic acid staining is presented as a challenge in the study of lesions of the cervix. It is hoped that intensive research in this field will yield promising results in recognizing the earliest stages of malignant and premalignant lesions of the cervix when curing them is easily possible. It must be more than just coincidence or chance that this mosaic or papillary pattern of the cervical mucous membrane is almost always present in cases of carcinoma in situ. This pattern when associated with pregnancy has been found to persist after pregnancy.

The next problem is the significance of the mosaic pattern in those cases which are premalignant dyskeratosis or atypical basal hyperplasia. Some of these give malignant tissue growth patterns and others do not. Some of these have Class I and others Class V Papanicolaou smears. Where does cancer begin and upon what do we base our final diagnosis—colposcopic examination, Papanicolaou, biopsy, conization, tissue culture, or a combination of all of these?

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Atypical epithelial hyperplasia of the uterine cervix

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ATYPICAL epithelial hyperplasia histologically constitutes abnormality of the deep layers of the cervical squamous epithelium and is characterized by immature and atypical cells but with normal maturation toward the surface. Carcinoma in situ, on the other hand, involves the whole thickness of the epithelium and there is no maturation of surface cells. Atypical epithelial hyperplasia may be seen histologically in conjunction with in situ or invasive cervical cancer.[1, 3-5] It may also exist as an isolated lesion and produce malignant-appearing cells in cervical smears. The present work was undertaken as a prospective study to ascertain the clinical factors associated with the condition and to study the relationship between the histologic findings in the cytologic smear, the punch biopsy, and the cone biopsy. For this purpose, all patients found to have atypia, however slight, of the squamous epithelium obtained by punch biopsies were hospitalized for removal of additional tissue.

Patients

One hundred and four patients form the basis for this study. The initial cervical biopsies were taken for a number of reasons, including visible lesions and abnormal cytologic smears. The majority of these patients were obtained from the Obstetric and Gynecologic Clinic and were pregnant, puerperal, or had significant gynecologic symptoms. A few patients were referred by other services of the Research and Educational Hospitals.

There were 82 Negro and 22 white women in this series. Sixteen were nulliparous and 88 were parous. Their ages ranged between 17 and 74 years with an average of 34.4; approximately 60 per cent were in the third decade of life. Twenty-five women were found to have atypical epithelial hyperplasia during pregnancy or 6 weeks puerperally.[2] Of these, 11 were intrapartum and 14 were postpartum patients. These women comprise slightly less than 25 per cent of the entire group. The symptoms and findings presented by these patients are recorded in Table I. Almost three fourths of these women had cervicitis or cervical erosions. Erosion was found in all pregnant and puerperal women.

Method

Cytologic smears were prepared from all but 3 patients at the initial visit, and findings were reported according to the classification of Papanicolaou. Punch biopsies were taken with the Gaylor biopsy forceps and four quadrants were usually sampled. Visible lesions were biopsied when present and constituted one of the quadrant samples. Diagnostic cone biopsy of the cervix involved the removal of the entire squamocolumnar junction and an adjacent centimeter of endocervix. The epithelium of the upper endocervical surface was obtained by curettage. Eight to twelve representative blocks were

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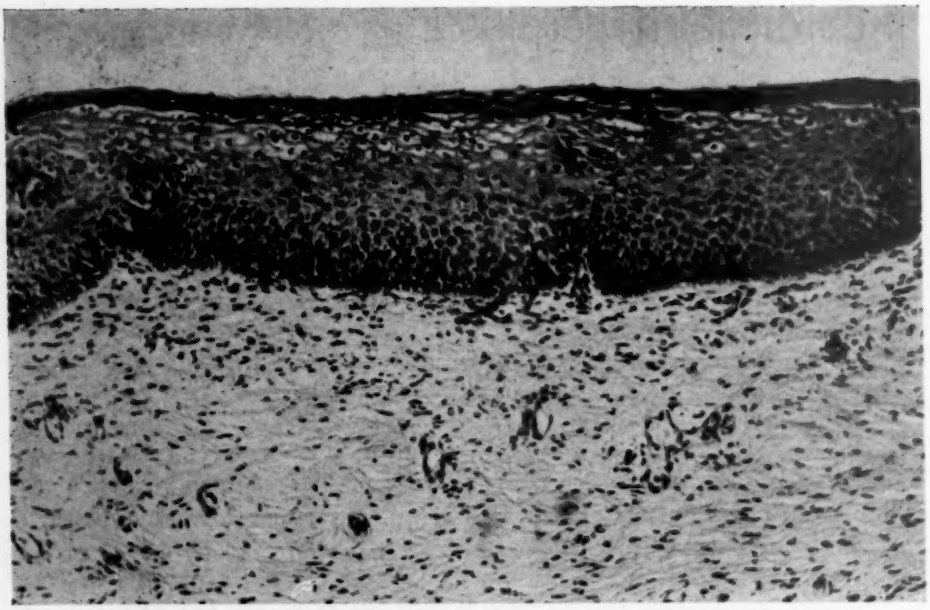

Fig. 1. Mild atypical epithelial hyperplasia. The basal cells and cells of the lower third of the epithelium are crowded and have large, dark nuclei. Cells mature as they approach the surface. Occasional cells are in mitosis. Scattered atypical cells are seen near the surface. (×170; reduced ¼.)

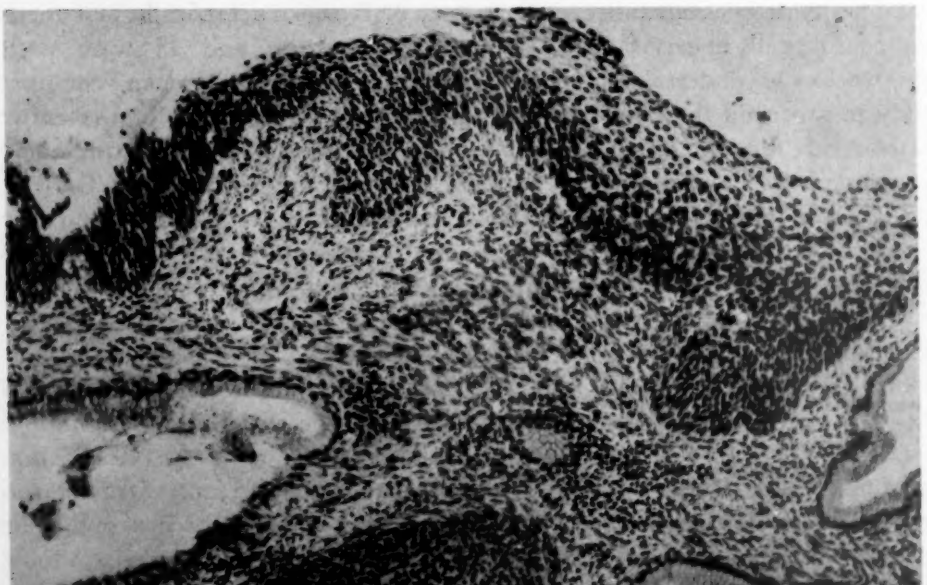

Fig. 2. Moderate atypical epithelial hyperplasia. The atypical cells involve predominantly the lower two thirds of the epithelium. These cells vary in size, have hyperchromatic nuclei, and generally have only a thin rim of cytoplasm. Occasional cells are in mitosis. Glands are similarly involved. A possible source of error in grading is seen on the left where detachment of superficial cells gives the appearance to the remaining epithelium of full thickness involvement. (×135; reduced ⅓.)

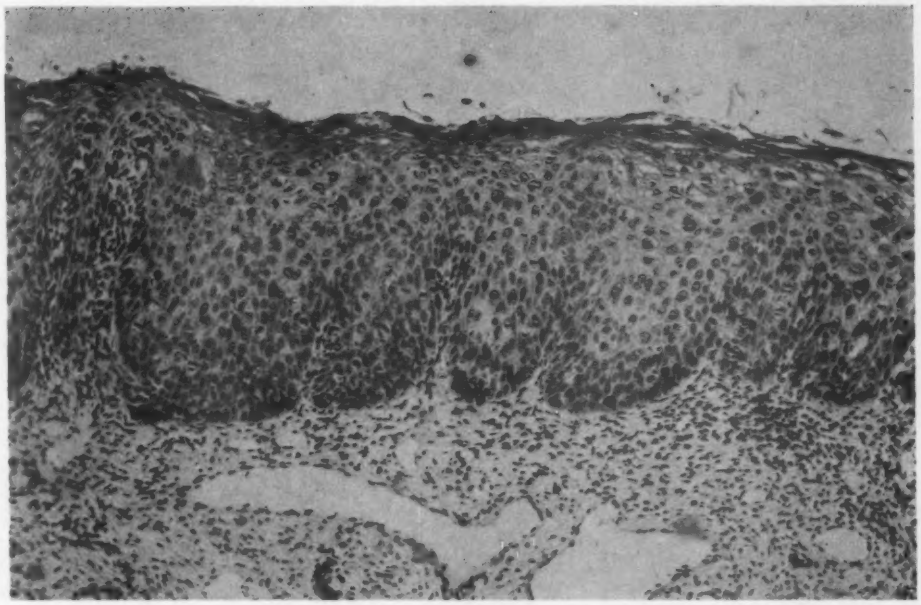

Fig. 3. Moderate atypical epithelial hyperplasia. Although atypical cells involve mainly the lower third of the epithelium, the lesion is upgraded because a number of highly atypical cells are found close to the surface. The preservation of cellular maturation is noteworthy in the presence of numerous atypical cells. (×170; reduced ¼.)

prepared from the cone biopsy specimens. All specimens were graded into three groups on the basis of histologic appearance. Two factors were considered in grading, namely, the extent of the epithelium involved by abnormal cells and the degree of cellular atypia. Lesions were considered mild (Fig. 1) if only the deepest one third of the epithelium was involved, moderate if the abnormality occupied one third to two thirds of the thickness of the epithelium (Figs. 2 and 3), and advanced if more than two thirds was involved (Figs. 4, 5, and 6). Mild and moderate lesions were graded one step upward if nuclear abnormalities were especially marked.

Results

Of 101 cytologic smears, 42 were interpreted as Class I, 29 Class II, 24 Class III, and 6 Class IV. Of 42 patients with Class I smears, 10 had advanced atypical changes in punch biopsies, and the subsequent cone biopsies contained 13 advanced lesions and 1 carcinoma in situ. Of 29 patients with Class II smears, 11 punch biopsies contained advanced change, and in the subsequent cone biopsies there were 11 advanced lesions and one carcinoma in situ. Of 24 patients with Class III smears, 15 had advanced atypia in punch biopsies, and in the cone biopsies there were 13 advanced lesions, 1 carcinoma in situ, and 1 invasive carcinoma. Of 6 patients with Class IV smears, 5 had advanced changes in punch biopsies, and in the cone biopsies there was 1 carcinoma in situ and another in situ lesion with possible early invasion. All 6 in situ carcinomas and the single invasive carcinoma were found in patients in whom punch biopsy specimens contained advanced atypical epithelial hyperplasia. These patients constitute 17 per cent of the group with advanced lesions.

Two of the 6 cases of carcinoma in situ were detected at the time of the postpartum

Table I. Symptoms and findings

Cervicitis, erosion	73
Bleeding, contact	11
Menstrual (abnormal)	24
Intermenstrual	32
Cervix (enlarged)	12
Vaginal discharge	14

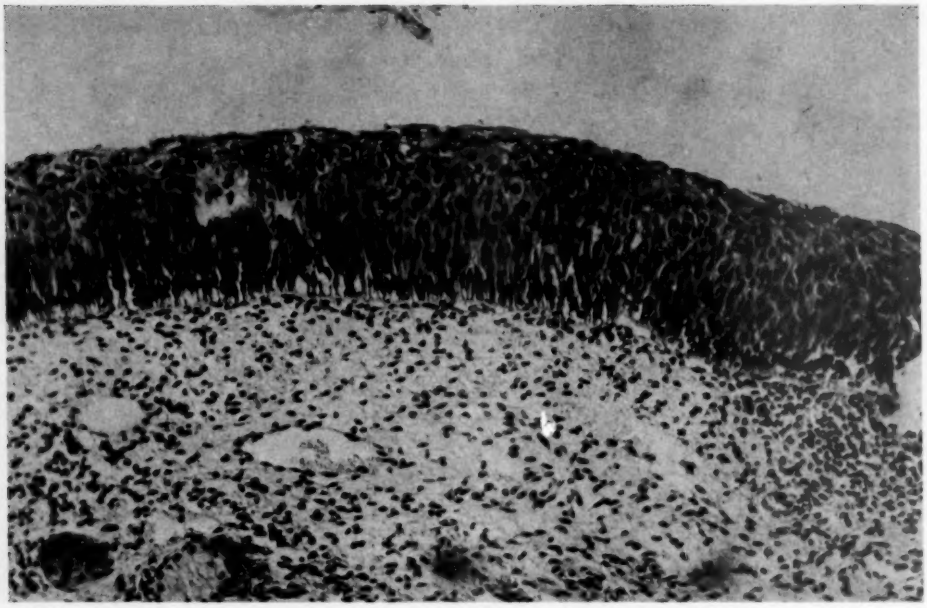

Fig. 4. Advanced atypical epithelial hyperplasia. Cellular maturation occurs but is incomplete. Cells are crowded and pleomorphic. The nuclei are dark and contain relatively large chromatin clumps. Mitotic figures are seen frequently. (×170; reduced ¼.)

visit by biopsy of cervical erosions. Both patients were 24 years of age and had 4 and 5 children, respectively. The cytologic smear of one of these women contained suspicious appearing cells but the smear of the other did not. All of the 4 remaining patients with carcinoma in situ had suspicious or malignant appearing cells in their smears and were 28, 33, 52, and 58 years of age. Five of the 6 women had cervical erosions, and all 6 had advanced atypical epithelial hyperplasia in the initial punch biopsy. The single patient of the entire group found to have an invasive carcinoma was 44 years of age, had a cervical erosion, and had a Class III smear.

Abnormal bleeding was encountered rather frequently but did not result from the atypical hyperplasia. Usually it could be explained on the basis of other gynecologic disease, such as myoma, cervicitis, and chronic pelvic inflammation. Cervicitis or cervical erosions were found in about three fourths of the patients and in all pregnant or puerperal patients and probably indicates that epithelial atypia tends to occur in the chronically infected cervix.

Study of exfoliated cells is responsible for the current interest in atypical epithelial hyperplasia and carcinoma in situ. However, a single cytologic specimen is not a perfect indicator of the presence of epithelial atypia. Only 5 of the 7 women found to have carcinoma had suspicious or malignant appearing cells in the original smears.

Conclusions

1. Seven of the 104 women with atypical epithelial hyperplasia proved to have in situ or invasive carcinoma. This exceeds expectancy and points to a relationship between the lesions. The atypical change is of special significance if abnormal cells occupy two thirds or more of the thickness of the epithelium and indicates the need for immediate further diagnostic study.

2. A single cytologic specimen is not adequate for finding all advanced lesions or intraepithelial carcinomas.

3. Atypical epithelial hyperplasia has no characteristic symptoms but is often associated with chronically infected and eroded cervices. The postpartum erosion should not be considered invariably benign because 2 of 6 intraepithelial carcinomas were found by biopsy of such lesions.

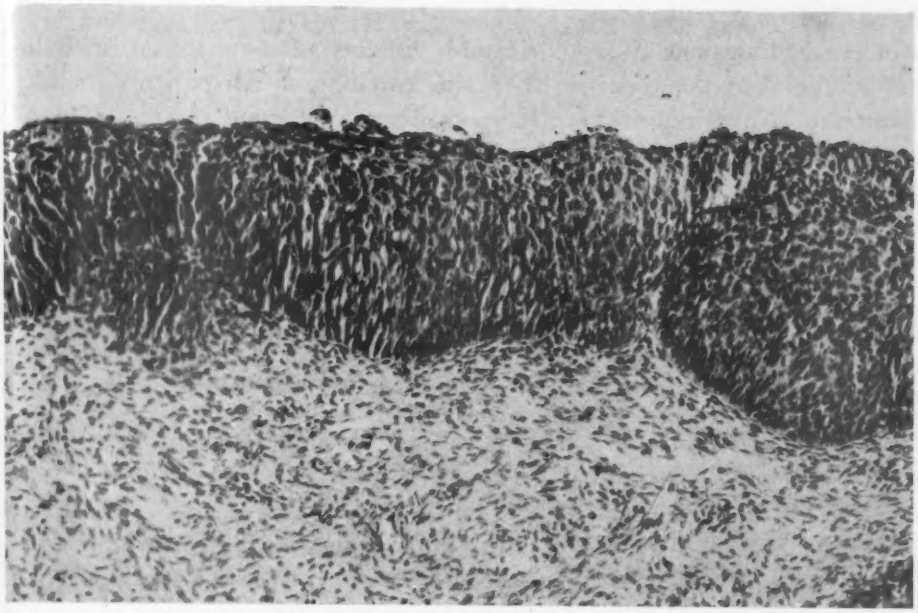

Fig. 5. Carcinoma in situ. There is complete loss of the usual epithelial pattern. The cells are pleomorphic. The nuclei are large, irregular, and hyperchromatic. Atypical cells involve the full thickness of the epithelium. Mitotic figures are frequent. There is no evidence of invasion. (×200; reduced ¼.)

Summary

One hundred and four patients with atypical epithelial hyperplasia were studied to ascertain the relationship to cervical carcinoma and to study the clinical factors associated with the condition and the relationship between the findings in the cytologic smear, punch biopsy, and cone biopsy.

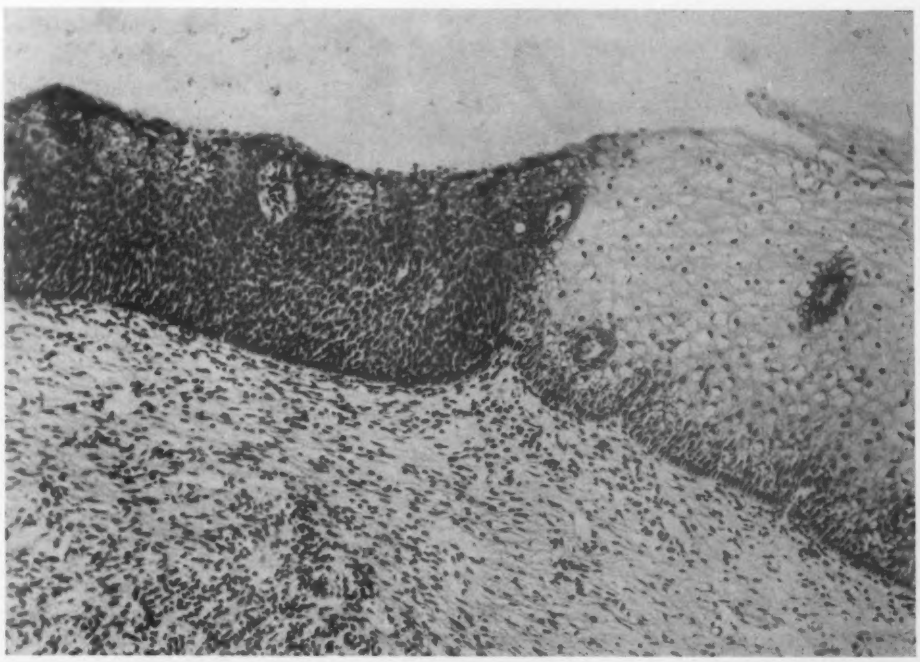

Fig. 6. Advanced atypical epithelial hyperplasia showing an abrupt transition between normal and abnormal epithelium. A similar transition zone is seen often with carcinoma in situ. (×140; reduced ⅓.)

Approximately three fourths of the patients had cervicitis or cervical erosions and 25 were pregnant or puerperal at the time the lesions were discovered. No symptoms or findings were characteristic of the condition and most symptoms could be explained on the basis of the associated diseases.

The cytologic smear failed to detect a considerable number of these lesions, including 2 in situ carcinomas. All patients found to have carcinoma in cone biopsies had advanced atypical epithelial hyperplasia in preceding punch biopsies.

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Walthard cell rest of the cervix uteri

Report of a case

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WALTHARD cell rests have been found in the ovary, the ovarian hilus, the mesovarium, the Fallopian tubal serosa, the mesosalpinx, and the broad ligament, but none have been described within the uterus or the cervix uteri. In the following case, a typical Walthard cell rest was incidentally found deep within the cervical stroma near a mesonephric tubule. A suggestion is made of possible Walthard cell rest derivation from mesonephric remnants.

W. M., a 56-year-old white gravida ii, para i, whose past history is unremarkable, was admitted to the Harkness Pavilion of the Columbia-Presbyterian Medical Center on Aug. 6, 1960, one week following a fall on her buttocks. In the week which followed, she had intermittent lower abdominal pain, mild diarrhea, and some nonspecific urinary tract symptoms. On the day of admission, there was a sudden onset of severe, nonremitting lower abdominal pain. Examination disclosed a grapefruit-sized right adnexal and cul-de-sac mass which was exquisitely tender. The preoperative differential diagnosis was torsion of an ovarian cyst or degenerating fibromyoma. A celiotomy was performed which revealed about 200 ml. of sanguineous peritoneal fluid and an ovoid, 10 by 8 by 8 cm., dusky, hemorrhagic solid tumor replacing the right ovary. Its pedicle was twisted through 180 degrees. Complete hysterectomy and bilateral salpingo-oophorectomy were performed and the patient had an uneventful recovery.

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Pathologic report. The cervix and uterus together weighed 60 grams. The cervix was grossly unremarkable; no cysts or unusual nodules were seen within its stroma. The uterus was small and the endometrium was thin and showed evidence of recent curettage. The Fallopian tubes were thin and atrophic, but patent. The left ovary was multilobular and its surface was pale. No cysts were seen on its surface or inside when it was sectioned. The right ovarian mass, submitted separately, measured 10 by 8 by 8 cm. and weighed 200 grams. It was slightly irregular, ovoid, and hemorrhagic. There was a small, white, whorled, homogeneous, apparently viable, mass of tissue within it. There were no cystic areas within the tumor.

Microscopic examination of the cervix revealed a well-preserved squamous epithelium and a partially eroded endocervical epithelium. There was a moderate infiltration of the cervical stroma by lymphocytes. One and one-half centimeters superior to the external cervical os and approximately 0.5 cm. from the origin of the parametrium was a well-demarcated group of elongated to polyhedral cells with clear cytoplasm and uniform, small, hyperchromatic nuclei. The center of this cellular aggregation was cystic. The connective tissue around this cell rest was condensed. The entire lesion was located within the stroma of the cervix (Figs. 1-3). The block containing this Walthard cell rest was completely sectioned, but no further evidence of it could be obtained. Several additional sections of the same area of the endocervix were prepared. They showed a ductile structure located within the cervical stroma. The lining epithelium of this duct was made up of ciliated cuboidal cells with clear cytoplasm and nonciliated low columnar rather dark-staining cells.

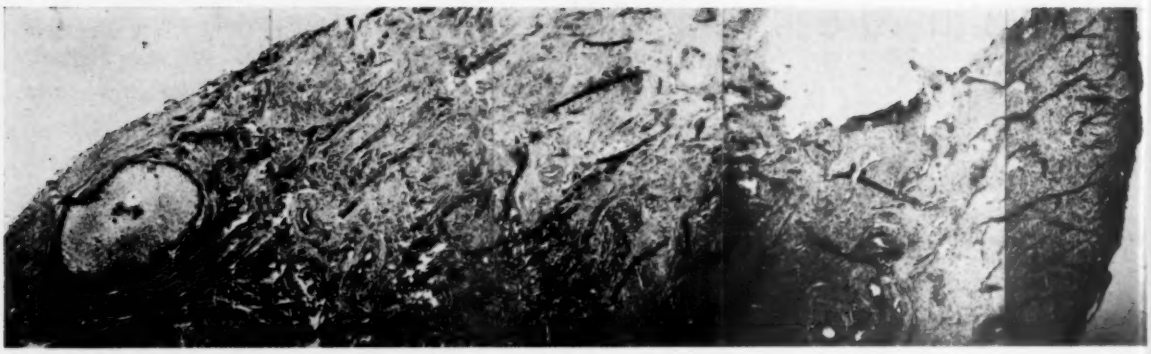

Fig. 1. Low magnification and reconstruction of the cervix, showing squamous epithelium to the right and stromal localization of the Walthard cell rest to the left.

The basement membrane was easily discernible even in the hematoxylin-eosin stain. This structure was interpreted to be a mesonephric tubule.

The endometrium, myometrium, and Fallopian tubes were atrophic. There was acute perisalpingitis on the right. The left ovary was atrophic and contained a papillary serous cystadenoma of microscopic size. The nonhemorrhagic portion of the right ovarian mass had the typical appearance of a fibroma; the remainder of it was necrotic and hemorrhagic. The ovarian vein on the right was thrombosed. The final pathologic diagnoses were: twisted ovarial fibroma, right, with hemorrhagic necrosis; Walthard cell rest, cervix; mesonephric tubule, cervix.

Comment

There has been considerable disagreement betwen investigators concerning the histogenesis of the Walthard cell rest. Four principal theories have been championed[1]: (1) derivation from celomic epithelium, as a developmental anomaly,[2] (2) origin from invaginations of peritoneum in response to inflammation and unknown factors,[3] (3) genesis from the ovarian germinal epithelium or follicle,[4] (4) derivation from other tissues and embryonic rests not specified.[5]

The exact incidence and distribution of Walthard cell rests have been infrequently investigated. Mueller[5] reported an incidence of 12 per cent in the 251 adnexa he examined, but he did not specify their exact locations. In single sections of normal Fallopian tubes and ovaries, Danforth[2] found Walthard cell rests in 16 per cent of 350 Fallopian tubes and in 5 per cent of 100 ovaries. Neither investigator reported finding a Walthard cell rest in the broad ligament or the cervix. We are unable to find any published accounts of finding them in this location.

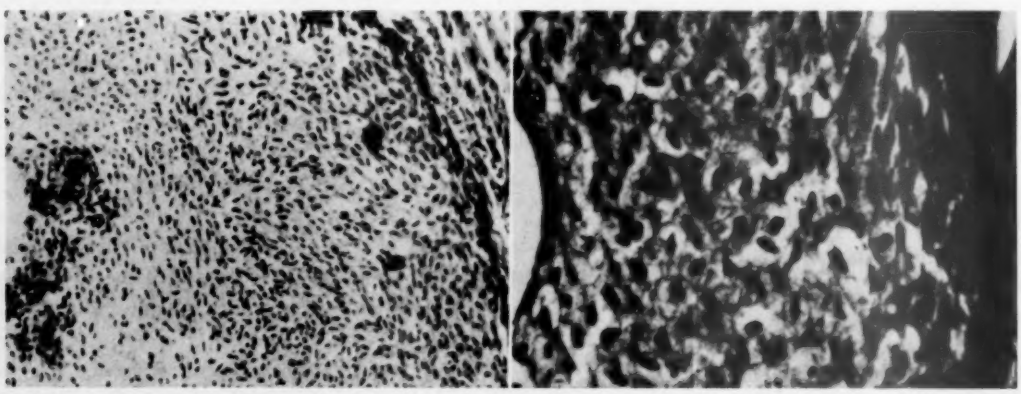

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Fig. 2. Medium magnification of the Walthard cell rest, showing clear cells with round to ovoid nuclei and pronounced connective tissue condensation on the periphery.

Fig. 3. High magnification of the same area showing cellular detail.

Fig. 4. Low magnification and reconstruction of the cervix, showing squamous epithelium to the right and stromal localization of the mesonephric tubule to the left at approximately the same level and localization as shown in Fig. 1.

The embryologic development of the female genital tract and its accessory structures have been well reviewed,[6, 7] and the occurrence of mesonephric, or Wolffian and paramesonephric, or Müllerian epithelial remnants in the broad ligament and the connective tissue of the cervix and vagina have been lucidly explained and definitively studied by Gardner and associates[8] and by Huffman.[7] Some of these remnants remain dormant; others become cystic or may undergo benign or malignant neoplasia.[10] In general, the mesonephric tubules are found in the ovarian hilum or the mesovarium. The mesonephric duct parallels the Fallopian tube and the lateral border of the uterus, cervix, and vagina. Nonneoplastic mesonephric tubular remnants were found by Huffman[7] in 5 of 1,192 surgical specimens of the cervix. The actual incidence is probably between 20 per cent and 40 per cent in the cervix.[7] Huffman's figure is probably quite accurate, however, for the incidence in ordinary sections taken from surgical specimens. Paramesonephric or Müllerian remnants are generally encountered in the mesovarium and occasionally in the broad ligament.[8] Mesonephric and paramesonephric elements are usually histologically well differentiated, although the distinction is sometimes impossible.[8, 9]

In the case presented, we have found both a Walthard cell rest and a mesonephric tubule located within the cervical stroma on the same side and at approximately the same level (Figs. 1 and 4). The appearance

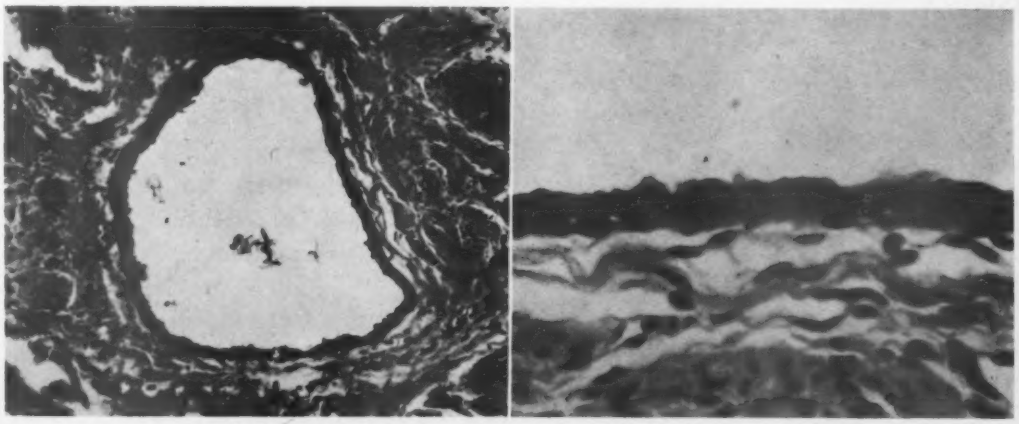

Fig. 5. Medium magnification of the mesonephric tubule surrounded by cervical stroma.

Fig. 6. High magnification of the mesonephric tubule lining epithelium. Clear cells with cilia and low columnar epithelial cells with dark nuclei, resting upon a prominent basement membrane, are evident.

of a mesonephric tubule in a routine section of the cervix is unusual.[7] A Walthard cell rest in the cervix has not, until now, been reported. It would seem to us that their concomitant presence and propinquity are difficult to explain on the basis of chance alone. As previously mentioned, the explanation for the mesonephric tubule located within the cervix is based primarily upon the embryologic development of the endocervix and the mesonephric duct and needs no further explanation. As to the presence and histogenesis of the Walthard cell rest within the stroma of the endocervix, it could hardly be explained by either the peritoneal or germinal inclusion theories. Derivation from anomalous development of celomic epithelium is, we feel, an irrefutable but not definite enough explanation. Absence of such rests in any of the other areas of the peritoneal and pleural cavities, or their celomic derivatives, represents indirect evidence against this hypothesis. We are left then with the last theory—development from other tissue or other embryologic rests. With the histologic demonstration of a mesonephric tubule in the vicinity of a Walthard cell rest, we hypothesize that the latter may be derived from the former, although by no means do we claim to have proved it, since we could not prove or disprove continuity between the two. Through a process of metaplasia, the epithelial cells of mesonephric tubules may proliferate eventually to structures similar, if not identical, to the Walthard cell rests.

Summary

1. A case of a Walthard cell rest of the cervix is presented.

2. A mesonephric tubule near this Walthard rest was also demonstrated.

3. The possibility of a mesonephric origin of Walthard cell rests is discussed.

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Trauma to the internal cervical os during dilatation for diagnostic curettage

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THE diagnostic curettage is a fundamental procedure in the practice of gynecology. Most of the pitfalls, such as perforation and infection, are well known and have been thoroughly studied. A search of the literature, however, has failed to reveal a description of what appears to be a common traumatic injury to the internal cervical os during the process of dilatation for routine diagnostic curettage. This injury has been repeatedly observed in our laboratory in uteri removed after preliminary curettage. The purpose of this paper is to describe this injury.

Materials

A consecutive series of uteri removed after preliminary dilatation and curettage at Sloane Hospital was collected. All specimens were inspected for evidence of trauma to the internal os. Hegar dilators were used in all cases. The specimens were opened along the anterior wall and the area of the internal os was inspected. Gross tears were recorded as to location, length, and depth. Injuries were classified as over 2 mm. in depth or over 5 mm. in depth. Tears grossly through the specimen were not classified separately because of the considerable variation of paracervical tissue received.

Histological sections of some of these tears were obtained by tying the specimen back together, amputating the cervix at the level of the tear, and fixing in formalin prior to blocking. Data pertaining to the patient's age, parity, menstrual pattern, and final diagnosis were obtained from the charts. The endometrium obtained during the curettage was reviewed and classified as to stage of menstrual cycle. All data were analyzed for statistical significance by the chi square test by Dr. Varma of the Columbia University School of Public Health.

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Findings

Trauma to the internal os varied from superficial abrasions to complete tears through the fibromuscular tissue into the paracervical blood vessels and lymphatics (Figs. 1 to 5). Of the 154 specimens, 60, or 39 ± 6.8 per cent, were found to have tears over 2 mm. in depth; 34, or 22 ± 6.8 per cent, had tears over 5 mm. in depth or through the specimen grossly (Table I). These tears occurred laterally in all but 3 cases, where complete

Table I. Incidence of tears of the internal cervical os

	No.	*%*
Total cases	154	
Tears over 2 mm.	60	39
Tears over 5 mm.	34	22

Table II. Influence of parity

	Nulliparous		*Parous*	
	No.	*%*	*No.*	*%*
Total	41		113	
Tears over 2 mm.	11	27	49	43
Tears over 5 mm.	7	17	27	23

perforations occurred along the posterior wall. All had the same characteristic configuration of a longitudinal split beginning in the cervical canal, becoming deepest at the level of the anatomical internal os, and tapering off again in the lower uterine segment to give the opened defect the form of a boatlike fossa. The lateral tears were evenly distributed with respect to side: 18 on the left, 20 on the right, and 19 bilateral.

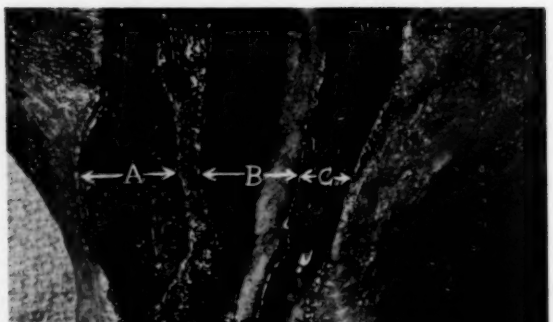

Fig. 1. Typical appearance of a deep tear at the level of the internal cervical os *(A)*. Note its depth (8 mm.), location (along the right lateral wall), and boatlike shape. The rough walls are in contrast to a fresh cut made in comparison in the posterior cervical wall *(B)* and normal endocervical epithelium *(C)*.

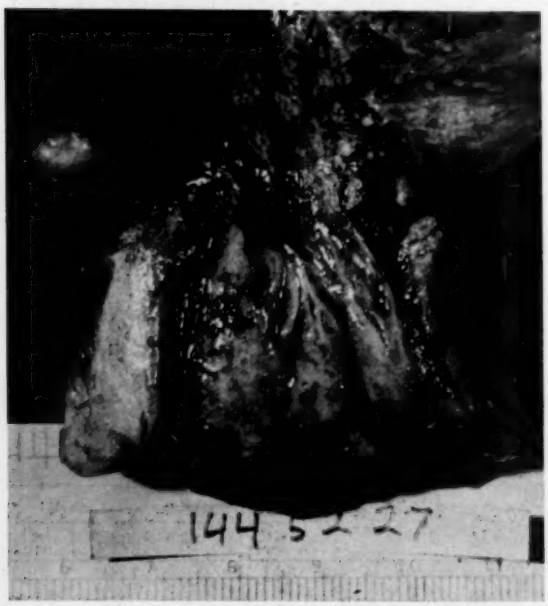

Fig. 2. A smaller tear at the internal os, again in the characteristic lateral position (5 mm.).

Table III. Tears of the internal os in postmenopausal patients

	No.	*%*
Total	22	
Tears over 2 mm.	11	50
Tears over 5 mm.	8	36

With trichrome and reticulum stains, no discernible difference in the histological appearance of the torn specimens was found compared to untorn ones. This was true with respect to fibrous connective tissue, elastic tissue, and smooth muscle.

The patients were studied with respect to parity and age. As is shown in Table II, there was a tendency for nulliparous cervices to tear less frequently than parous, but this was not found to be statistically significant. The postmenopausal patients were not found to be different from the group as a whole with respect to tears (Table III).

The final diagnosis was found to bear no relation to the injury. It was occasionally observed that uteri enlarged by fibroids had large intact cervices, probably as a result of the general hypertrophy of the organ. The day of the menstrual cycle on which the dilatation was done, as calculated from the last menstrual period, was also found to have no relation to the occurrence of tears. This is due to the fact that most of the patients had considerable menstrual irregularities, making the last menstrual period an unreliable guide. Therefore, the endometrium obtained was used as a guide to the hormonal environment of the cervix at the time of dilatation. Again, there was no discernible trend when analysis was done with respect to "secretory" versus "proliferative" alone. Since the cervix has been shown by hysterocervicogram to be most distensible at the time of ovulation and during menstruation,[1, 2] the specimens with curettings showing early basilar vacuolization of endometrial glands as well as hemorrhagic late secretory endometrium were analyzed separately. Ta-

Fig. 3. A gross cross-section of a tear in the right lateral wall going completely through the cervical stroma but held together by paracervical tissue.

ble IV again shows that tears occurred in both these stages of the cycle with no statistically different frequency than in the group as a whole. Finally, extremes of hormonal influence were evaluated by comparing the results of dilatation in the presence of atrophic endometrium with those with hyperplastic proliferative endometrium (Table V). The absence of tears in the hyperplastic group was found to be statistically significant at the 1 per cent level. These results suggest that cervices under prolonged unopposed estrogenic stimulation are more elastic than the average.

Comment

This series of injuries seen in hysterectomy specimens is presented as an indication of injuries occurring during curettages in general. The possibility arises that a curettage done immediately prior to a hysterectomy, as in the majority of these cases, is a more briskly done procedure than a diagnostic curettage alone, that therefore the injuries described would not occur in the latter procedure. However, several specimens were those of uteri removed several days after a purely diagnostic curettage, where the curettings or cervical findings indicated the subsequent hysterectomy. The tears found in these specimens were similar to those found in the rest of the series (see Fig. 6 as an example). Also, it was our personal observation of the ward and private physicians doing these operations that at Sloane Hospital dilatation was a fairly uniform procedure with the doctor allowing 5 to 10 seconds per

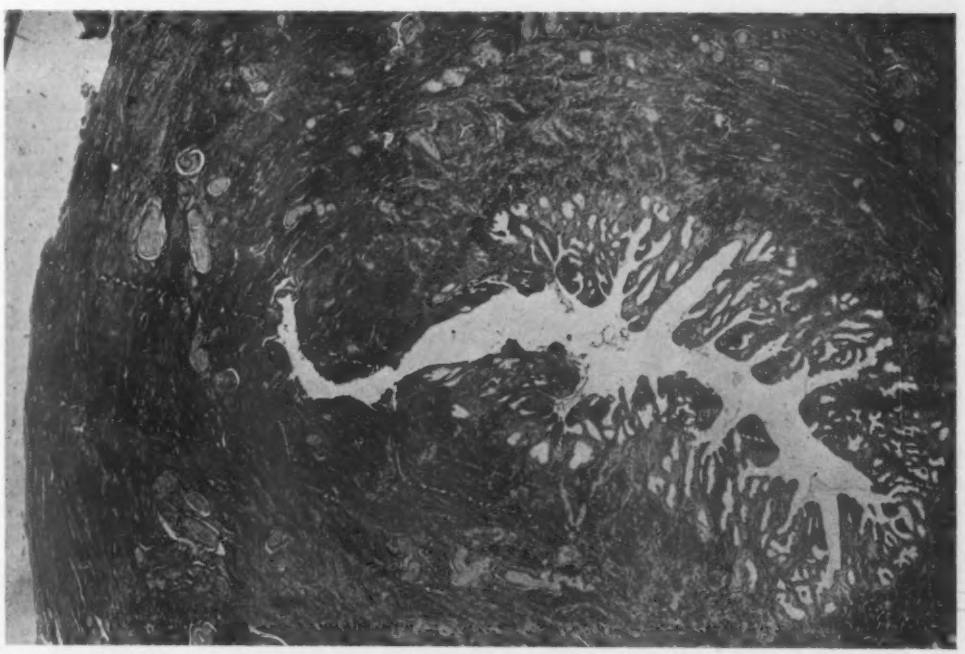

Fig. 4. Histological section through an unopened specimen showing a tear in the lateral wall near the internal os going halfway through the cervical stroma. (×10; reduced ¼.)

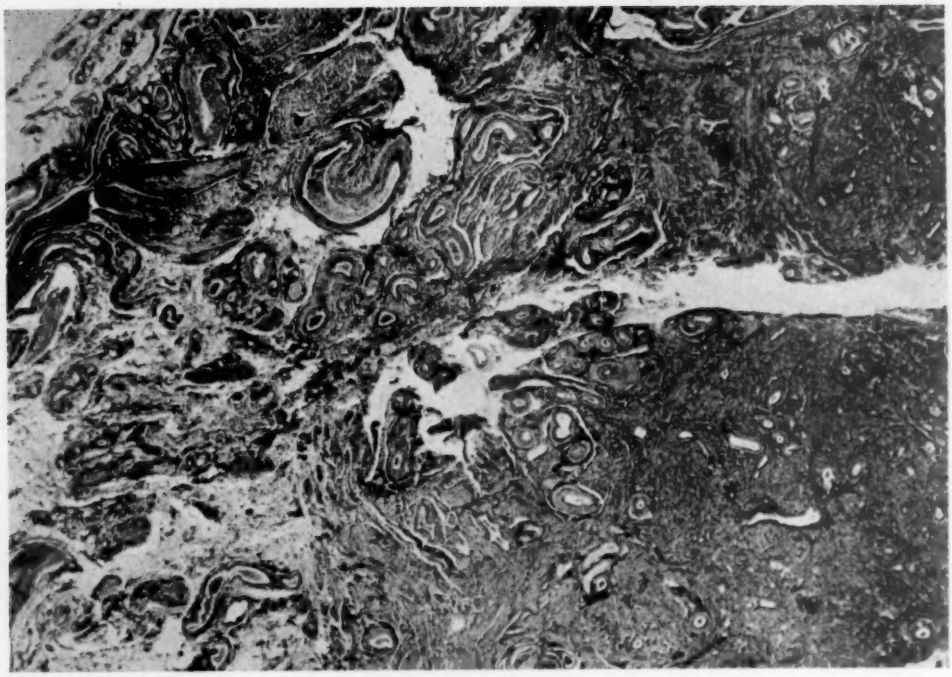

Fig. 5. Histological section through the lateral cervical wall showing a tear extending from the cervical canal (far right) through the stroma and well into the paracervical lymphatics and blood vessels. (×25; reduced ¼.)

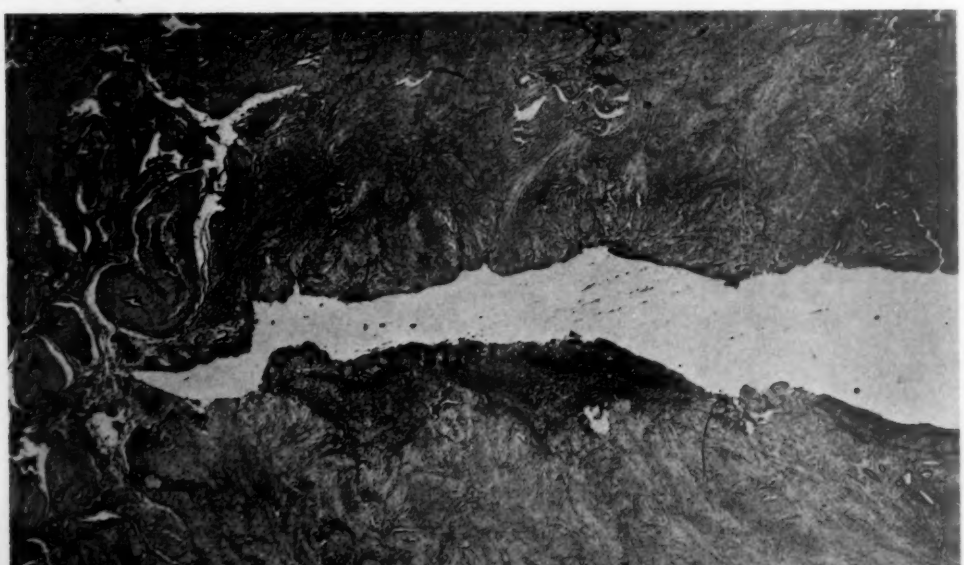

Fig. 6. Early wound healing in a tear. This patient had undergone a curettage 3 days prior to hysterectomy. The tear extended from the cervical canal (far right) through the cervix into the parametrial vessels. Early organization is seen in the blood clot. (×15; reduced ¼.)

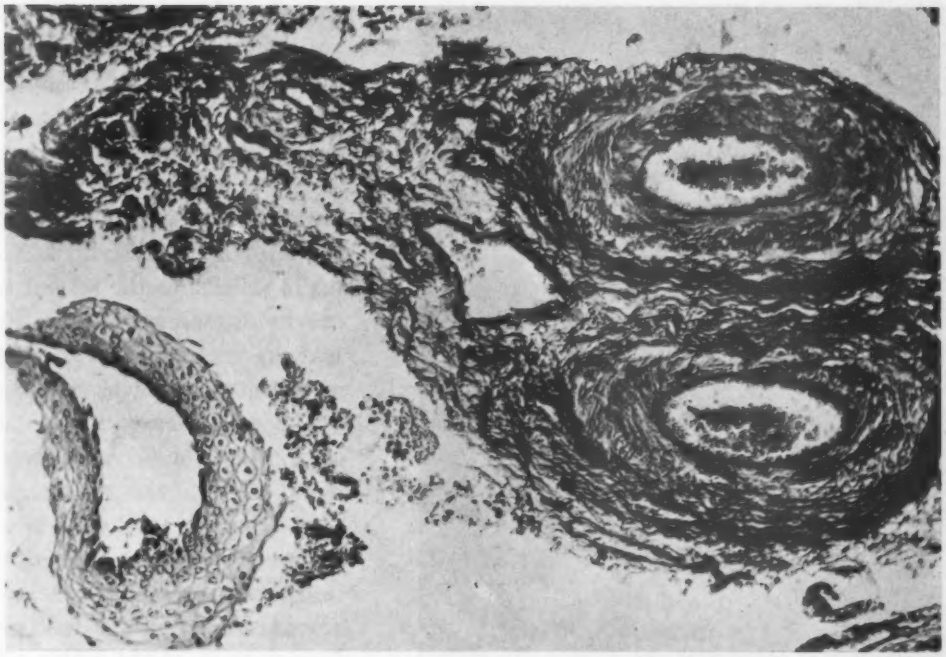

Fig. 7. Squamous epithelium (lower left) near paracervical lymphatics and vessels This is a magnification of the central portion of Fig. 5. (×100; reduced ¼.)

dilator and usually proceeding to the largest dilator available. This held true for both diagnostic and prehysterectomy curettages. Thus, the assumption that this series is a valid sample of injuries occurring during diagnostic curettages seems to be warranted.

The data indicate that one cannot predict in a given patient whether or not such a tear will occur. This unpredictability suggests strongly that the surgeon should be prepared to alter the routine technique of dilatation. The sudden "give" encountered during dilatation may well represent the occurrence of these tears. To avoid this, when stiff resistance is encountered at the level of the internal os perhaps a more prolonged insertion of the dilator, up to 20 or 30 seconds, should be considered to allow the tissue to stretch more slowly. It is certainly not necessary in every diagnostic curettage to dilate up to the largest Hegar in order to insert a clamp and a medium-sized curette.

In the countries where therapeutic abortions are widely performed, clinicians are aware of the dangers of laceration of the internal cervical os during dilatation of the

Table IV. Tears of the internal os during different parts of the menstrual cycle

	Midcycle		*Menstrual*	
	No.	*%*	*No.*	*%*
Total	12		21	
Over 2 mm.	8	66	6	28
Over 5 mm.	4	33	4	19

Table V. Tears of the internal os during extremes of estrogenic stimulation

	Hyperplasia		*Atrophy*	
	No.	*%*	*No.*	*%*
Total	14		15	
Over 2 mm.	0	0	9	60
Over 5 mm.	0	0	9	60

Table VI. Summary of analysis of possible factors in cervical tears

	Over 2 mm. (%)	*Over 5 mm. (%)*
Total series	39	22
Nulliparity	27	17
Parity	43	23
Midcycle	66	33
Menstrual	28	19
Hyperplasia	0	0
Atrophy	60	60

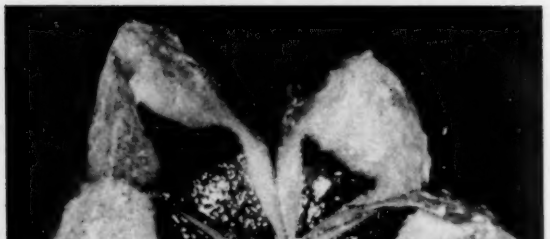

Fig. 8. Deep tear and perforation in the right lateral wall of the internal os. The upper edge of this tear was felt on curettage to represent a submucous fibroid, for which this hysterectomy was performed.

pregnant cervix. The resultant hemorrhage produced by this injury in pregnancy has brought it to their attention in many studies.[3] However, the literature has no study of this injury in the nonpregnant cervix, although a few authors[4-6] do list it as a possible danger in the routine curettage.

Perhaps this is because, in the vast majority of cases, these tears produce no signs. Bleeding was not alarming in this series even in those cases where tears had reached the paracervical vessels. Moreover, healing is probably adequate and leaves a plate of scar tissue similar to the rest of the fibromuscular cervix anatomically and functionally. This was suggested by the findings in a few specimens removed several days after coning biopsies for intraepithelial carcinoma of the cervix. In these, early organization of the blood clot in the narrow area of tear was seen (Fig. 6).

However, there are several theoretical complications of such tears that should be considered. First, the tear may be an avenue for infection of the paracervical tissues. This might explain the occasional occurrence of unilateral postcurettage parametritis. Parametrial hemorrhage and hematoma formation could similarly occur. Next, the tear could be an avenue for seeding of carcinomatous tissue in the paracervical lymphatics. This is illustrated in Fig. 7, showing a fragment of squamous, undoubtedly cervical, epithelium in the base of such a tear surrounded by blood vessels and lymphatics. The orientation of the fragment suggests that it was brought there prior to sectioning, and this was probably present in the specimen as

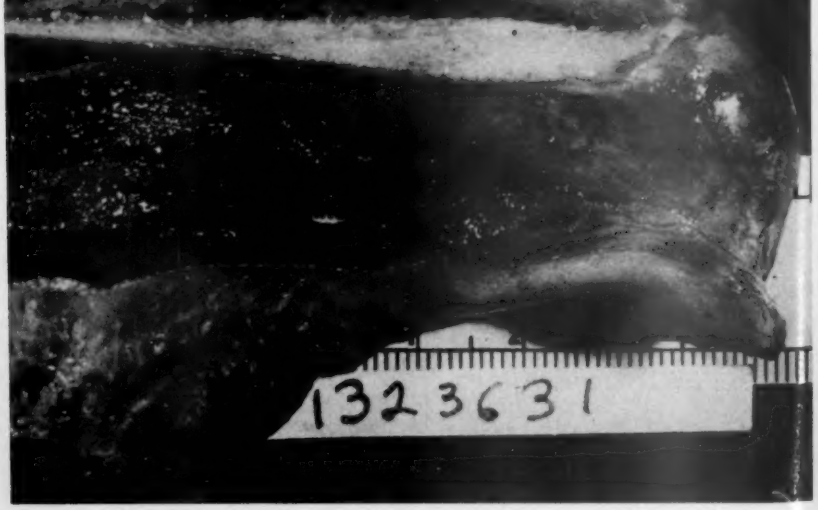

Fig. 9. Close-up of laceration in Fig. 8. Bleeding was minimal during the curettage, despite the complete tear.

received rather than an artifact of processing.

These tears may be a factor in the etiology of the incompetent cervical os. It is possible that by not healing completely these tears could produce defects in the sphincteric mechanism of the isthmus, rendering it incapable of retaining gravid uterine contents. Finally, a very real pitfall of this injury is that of misinterpretation at the time of curettage. Should the curette be run over the tear, the sensation produced by the sudden drop into the defect could be interpreted as representing a submucous fibroid. There was one hysterectomy performed in this series as a result of this misinterpretation (Figs. 8 and 9). The curettage in this case was done by two experienced clinicians, and discussion with them revealed that the suspected location of the submucous fibroid was actually the site of the tear. Since the completion of this series, another similar case has occurred.

Summary and conclusions

A series of 154 hysterectomy specimens from patients who had had curettages was examined for evidence of trauma to the internal cervical os area. Thirty-nine per cent of the specimens had tears at the internal os over 2 mm. in depth, and 22 per cent over 5 mm. There appeared to be no significant predisposing factors to the occurrence of these tears with respect to age, parity, underlying disease, or time of menstrual cycle. However, no tears occurred when hyperplastic proliferative endometrium was present (Table VI).

The possible significance of this injury with respect to spread of infection, hemorrhage, spread of carcinomatous tissue, etiology of the incompetent cervical os, and misinterpretation as a submucous fibroid is discussed. It is urged that the clinician be aware of the possibility of this injury occurring during a routine diagnostic dilatation and curettage. Should excessive resistance at the level of the internal os be encountered, adequate time should be allowed for a slower, more gentle dilatation of the tissues, and complete dilatation to the largest Hegar should be avoided.

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Conization and scarification as a treatment for cervical incompetency

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THE internal cervical os which is incompetent to retain a last-trimester pregnancy represents a clinical entity recognized with increasing frequency in recent years. Shirodkar,[1] McDonald,[2] and the Badens[3] have all introduced operations for the treatment of this condition; the various procedures are emergency measures for use during the middle trimester when the incompetence of the cervix is manifestly jeopardizing the continuation of the pregnancy. In contrast to these, the cervical repair first employed by Lash in 1941, and reported in 1950,[4] represents an elective procedure for use in the nonpregnant state. The present brief note records a small series of cases of this defect managed by another technique suitable for use in the nonpregnant.

The operation

In view of the fact that the two chief complications of electroconization of the cervix are hemorrhage (early) and stenosis (late), an attempt has been made to capitalize on the latter "complication" to achieve sufficient holding power in the cervix. The procedure followed has been shallow electroconization of the cervix followed by a rather heavy electrocauterization of the upper portion of the coned area. The coned area was packed with hemostatic sponges, but no gauze was placed through the internal os itself. Postoperative dilatations to prevent stenosis were scrupulously avoided, although in 2 instances gentle sounding was felt to be necessary. In one case additional lateral sutures had to be employed because of active bleeding on the fourth postoperative day.

The patients

The records of 6 women (8 pregnancies) treated since 1951 form the basis for this report. By the very nature of this operative approach to the problem, all of these women were nonpregnant when first seen. Accordingly, in each instance the diagnosis was based initially on the characteristic anamnesis. In all cases this included an initial term delivery; in 3 cases after a prolonged labor, in 3 after a labor of normal duration, and in 1 after a labor of unseemly brevity. Following this initial reproductive experience, 1 woman had had 1 unsuccessful pregnancy, 3 had had 2, 1 had experienced 3 reproductive failures, and 1 patient had made 4 unsuccessful attempts to achieve a viable fetus.

In all instances the hallmarks of the unsuccessful deliveries were: (a) their occurrence in the middle trimester and (b) their relative "silence." These patients characteristically had had ruptured membranes or had "dropped the pregnancy out" with minimal or no prodromal labor pains. Several of them had been informed by their attending physician that they were "almost ready to deliver" when first seen. Women who described a relatively normal labor with contractions for several hours which

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occurred at 6 or 7 months were excluded, as were women harboring myomas.

In 3 of the 6 patients roentgen confirmation was obtained as described by Lash.[5] Subsequently this procedure was abandoned since, if the selection was made strictly enough on the basis of history, the x-rays contributed little beyond a bill. In all cases a sound was passed with the typical absence of "grip" by the internal os and undue mobility at this level.

Results

The 6 patients are known to have produced 8 living near-term babies ranging in weight from 2,530 to 3,300 grams, with a duration of pregnancy from 37 weeks (1 case) to 41 weeks (2 cases). In each instance the first postoperative pregnancy resulted in a viable child. One additional subsequent pregnancy ended in a first-trimester abortion, and it must be stressed that the follow-up data on 3 of the women are of such tenuous nature that a postpartum reversion to the preconization status cannot be excluded.

Of the 2 women who have each produced 2 viable babies postoperatively, I had personal contact with only one of these pregnancies and spent most of my time wishing I had "reinforced" the original procedure with deep endocervical cauterization post partum. The other pregnancy was not followed personally but according to the record was less precarious.

Complications

One finds casual mention in the literature that conization could lead to sterility.[6] No figures are cited to support this hypothesis, and, indeed, these would be difficult to achieve with conviction since one can think of at least 2 control series which would have to be constructed to approach statistical validity. The opposite view (that shallow conization can improve a woman's fertility status) is also expressed,[7] and this more nearly agrees with my experience. In any event, it should be stated that all of these women achieved pregnancy postoperatively without undue delay, and no patient in this series has been rendered sterile (this procedure has been carried out on 2 additional patients too recently to judge their fertility status).

Vaginal delivery after cervical conization, particularly after deliberate effort at scarification, presents potential hazards. All of the women under consideration here were delivered vaginally without major complication. In 2 instances, when effacement was complete with 3 to 5 cm. of dilatation at the external os, the internal os area remained a pinpoint scar. In both cases gentle but persistent digital pressure succeeded in breaking the adhesions of the cervical canal, and the internal os area "fell open" in the next two or three contractions.

One patient was subjected to a moderately extensive cervical repair immediately post partum, although the defect evident at that time was presumably no greater than the original laceration which had been present before the conization. The small number of cases in the current series, however, rules out valid conclusions as to the over-all safety of vaginal delivery. The present experience with a small number of these women would incline one to recommend close observation during labor rather than routine cesarean section.

Comment

Steinberg[8] in 1957 mentioned that in cervical incompetence "electro-coagulation of the internal orifice is indicated so that the resulting scar formation will produce an artificial stricture of the endocervix." This passing reference does not state whether or not he had performed such a procedure or what the results might have been. The collection of the present series had already been started at this point, and the chief difference between such blind coagulation in the general region of the internal cervical os and the present suggestion of preliminary shallow conization would seem to lie in the degree of exposure afforded to the upper canal. In most of the cases this has provided visual confirmation of the local tear.

There are, at the present time, a variety of procedures which will preserve the pregnancy of a woman with an incompetent internal cervical os. Most writers on this subject agree that strict bed rest during the latter half of pregnancy, and particularly bed rest in a mild degree of Trendelenburg position, would preserve the majority of such pregnancies without the need for surigcal intervention. This would lead to the conclusion that these operative procedures (Shirodkar, McDonald, Lash) are asked to provide a restraint which is equivalent to the force of gravity applied against the cervical canal.

Presumably the increment in force against the internal cervical os which results from assuming the upright position has multiple components. To the weight of the uterine contents must be added the transmitted weight of other abdominal organs; to the physiologic increase in antidiuresis (which presumed oxytocic effect) must be added the psychological tendency toward increased general activity. An attempt to measure this force experimentally has not proved to be particularly easy.

In a term patient in early labor, small polyethylene catheters were placed (a) transabdominally in the amniotic cavity and (b) transvaginally through the cervix to lie with its open end sutured at the level of the internal cervical os. Simultaneous pressure recordings were made with the Sanborn multigraph recorder while the patient was shifted from the recumbent to the upright position. Under these circumstances the baseline tonus between contractions showed an increase in pressure of 10 mm. Hg at the cervical catheter when the patient stood beside the bed. Unfortunately, this small of a shift in pressure requires a virtual guarantee that the open tip of the catheter lies at exactly the same level with respect to the recording instrument when the patient was in both positions. In so far as possible, this relationship was maintained, but the recording system is so sensitive that the only valid conclusion would be that in comparison with the pressure developed during a Braxton Hicks contraction, for example, the increased pressure resulting simply from standing up would seem to be of a small order of magnitude. It is entirely possible that many of the current surgical procedures add more strength to the cervix than is actually demanded.

Summary and conclusions

A small series of cases is reported in which electroconization with scarring of the upper canal has been employed as an interim procedure for restoring competence to an incompetent cervix.

I wish to express my appreciation to Dr. Luis Cibils for assistance in obtaining the pressure tracings.

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Surgical management of congenital atresia of the cervix

Case report and review of the literature

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CONGENITAL absence of communication between the uterus and the vagina in association with otherwise normal pelvic organs is a rare entity which appears infrequently in the gynecological literature. More commonly, rudimentary or absent cervix is associated with aplasia of the uterus, Fallopian tubes, and/or abnormalities of the vagina. In these latter cases, plastic reconstruction of a cervical canal offers very little hope for establishment of menstruation and future pregnancy.

Sherwood and Speed[1] divide congenital atresias of the cervix into three categories. These cases may present one of the following patterns:

1. Aplasia of the uterus with a nonfunctioning endometrium and amenorrhea.

2. Functioning endometrium, cyclic menstruation leading to hematometra, and enlargement of the uterus.

3. Normal uterus and adnexa with or without demonstrable retrograde menstruation through the Fallopian tubes; no enlargement of the uterus, but cyclic monthly lower abdominal pain.

The third category is extremely rare. We were able to find only 8 cases in the gynecological literature. The case presented herein falls in this group in which establishment of continuity of the genital tract, by successful surgical correction, altered what appeared to be a futile situation in a young woman. The alleviation of symptoms and the establishment of normal menstruation were achieved in addition to the creation of conditions favorable for future childbearing.

Table I demonstrates these 8 cases and ours in relation to age, symptoms, vaginal examination, findings at operation, surgical procedure, and follow-up.

K. H., an 18-year-old white girl, was admitted to the Methodist Hospital of Brooklyn on July 21, 1957, with a history of primary amenorrhea and cyclic abdominal cramps occurring at monthly intervals and increasing in severity, especially during the preceding year. The onset of cramps was at the age of 12. The last three episodes of pain, although generalized in the lower abdomen, were more severe in the left lower quadrant. The patient was a second year college student with an uneventful past history.

She was seen in the office for the first time 6 months prior to this admission. General history and physical examination were negative. Rectal findings appeared to be essentially normal.

The patient was followed in the office with repeated rectal examinations. She was given mild analgesics for pain and cyclic estrogen and progesterone therapy without the production of

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Table I. Cases as reported in the literature in relation to age, symptoms, findings, operative

Name	*Year*	*Age*	*Symptoms*	*Vaginal findings*	*Operative findings*
Ludwig[2]	1900	22	Primary amenorrhea and cyclic lower abdominal pains	Normal vagina with no demonstrable cervix	Blood in cul-de-sac; normal uterus; cervix not communicating with vagina
Berard[3]	1911	18	Primary amenorrhea and cyclic lower abdominal pains	Normal vagina with no demonstrable cervix	Uterus and left adnexa adherent to sigmoid; absence of cervix
Kermauner[4]	1924	19	Primary amenorrhea and cyclic lower abdominal pains	Normal vagina with no demonstrable cervix	Normal uterus; absence of cervix
Portes and Landrieu[5]	1938	25	Primary amenorrhea and cyclic lower abdominal pains	Normal vagina with no demonstrable cervix	Normal uterus; absence of cervix
Duyzings[6]	1939	23	Primary amenorrhea and cyclic lower abdominal pains	Normal vagina; rudimentary cervix but no entrance to uterine cavity	Normal uterus; no internal os could be found
Engelhens (quoted by Duyzings[6])	1939	—	Primary amenorrhea and cyclic lower abdominal pains	Normal vagina; rudimentary external os demonstrated	Normal uterus; cervix was a solid strand
Sherwood and Speed[1]	1941	19	Primary amenorrhea and cyclic lower abdominal pains	Normal vagina with no demonstrable cervix	Strandlike cervix between uterus and vagina; small blue-black areas on ovary, rectum and sigmoid
Rotter[7]	1958	16	Primary amenorrhea and cyclic lower abdominal pains	Slightly shortened vagina; no demonstrable cervix	Underdeveloped cervix with no connection to uterus or vagina
Authors	1958	18	Primary amenorrhea and cyclic lower abdominal pains	Normal vagina; rudimentary portio with no entrance to uterine cavity	Strandlike cervix connecting uterus to vagina; normal uterus; small blue-black areas on left ovary

*Microscopic examination of the excised rudimentary cervix showed absence of cervical canal.

bleeding or relief of symptoms. On July 21, 1957, she had an episode of severe abdominal pain. At this time hospitalization was advised for further evaluation.

Vaginal examination under anesthesia disclosed normally developed external genitals and vagina. A firm structure, about 7 to 8 mm. in diameter, was found in the vault of the vagina where the cervix should have been located. This structure presented a dimple, and it was assumed that this was the external os of a rudimentary cervix. However, a fine probe could not be introduced. This structure could be followed proximally on bimanual examination and it felt like a slender cord attached to a normal uterus. The left ovary was palpable.

The patient was discharged after 2 days with the diagnosis of maldevelopment and noncanalization of the cervix. She re-entered the hospital on Sept. 4, 1957, for plastic reconstruction of the cervical canal via the abdominal route.

Laboratory test results were as follows: erythrocyte count 4.5 million; hemoglobin level 15.8 per cent; leukocyte count 15,000 with normal differential; sedimentation rate 7; urinalysis essentially negative. A flat plate of the abdomen, taken preoperatively, revealed no abnormalities and no evidence of intra-abdominal calcification.

Procedure. With the patient under general anesthesia, a Pfannenstiel incision was made. The pelvic organs were exposed and both tubes and ovaries and the fundus appeared normal except for the presence of several blue-black areas on the left ovary simulating early endometrial implantations. Exploration of the abdominal organs disclosed no abnormalities except for a questionably small right kidney. Palpation beneath the bladder from the level of the

procedure, and follow-up

Surgical procedure	*Follow-up*
Hysterotomy and small trocar forcibly inserted through solid cervix into vagina; drain left in	None
Hysterectomy and left salpingo-oophorectomy	None
Hysterectomy	None
Hysterotomy and suturing of this site to opening in the vaginal vault	Normal menses one year, no pain
Hysterotomy and insertion of a drain into the vagina	Irregular menses for a short time
Excision of solid strand of cervix and suturing of hysterotomy site to an opening in the vaginal vault	Renewal of occlusion several months later, but reoperation successful
Strandlike cervix was cut transversely and excised*; hysterotomy site sutured to an opening in the vault; stem pessary left in	Pessary removal after 7 weeks, normal menses 3 years, no pain
1. Channel fashioned through underdeveloped cervix and polyethylene tube placed between vagina and uterus	1. Tube spontaneously eliminated after 3 weeks; operation unsuccessful
2. *Reoperation:* Anastomosis of hysterotomy site and opened vaginal vault over polyethylene tubing; split thickness graft over tube	2. Tube came out on the nineteenth day; 2 years' follow-up revealed normal menses
Channel made in underdeveloped cervix and two polyethylene tubes inserted between uterus and vagina	Tubes spontaneously eliminated after 11 weeks; cervicohysterogram revealed cervical canal present; normal menses to present with dysmenorrhea on the first day

internal os to the vagina revealed the absence of a normal cervix, but with a thin cordlike structure which resembled a markedly underdeveloped cervix.

The bladder flap was incised and reflected downward to expose the cordlike structure, which was found to be continuous with the uterus and extended into the vaginal vault. The anterior wall of the uterus was first incised transversely into the uterine cavity and then longitudinally. The uterine cavity appeared normal down to the internal os. The endometrial cavity was curetted through the uterine incision and the specimen sent to the laboratory. No canal was present in the cordlike cervix, which appeared to be a solid structure without opening at either the uterine or vaginal end.

Communication between the uterus and vagina was established as follows: The longitudinal incision in the anterior wall of the uterus was extended through the cordlike structure, care being taken not to bisect it, down to the vagina, and the vagina was entered. Two small polyethylene tubes were inserted in the vagina, then placed along the longitudinal incision in the cordlike structure and sutured to the endometrium with a plain No. 0 suture. The uterus and cordlike structure were then repaired over the polyethylene tubes with interrupted chromic No. 0 sutures. The bladder flap was then replaced over the lower uterine segment (Fig. 1).

Following closure of the abdomen, a vaginal examination was performed and it was noted that the polyethylene tubes were protruding into the vagina. These were sutured to what appeared to be a rudimentary portio vaginalis with a silk suture. The operation lasted 3 hours.

The patient received one pint of blood, and left the operating room in good condition.

On the eleventh day she was discharged from the hospital after an uneventful postoperative course. Pathological evaluation of the curettings obtained at the time of operation revealed endometrial hyperplasia.

The first menstrual period occurred on October 6, 31 days after the operation, and was quite heavy. It lasted 5 days, and was without pain. A second menstrual period occurred on November 13, and was similar in nature. On November 29, the patient was readmitted to the hospital because the polyethylene tubes slipped from the cervical canal after being in place 11 weeks. We felt that it was necessary to ascertain if the reconstructed cervical canal was still patent.

Accordingly, with the patient under general anesthesia, the newly formed cervical canal was entered with a very fine probe to a distance of 4 to 5 cm., following which 2 ml. of a contrast medium (Salpix) was inserted. The cervicohysterogram revealed reconstruction of a functioning, but somewhat small, cervical canal (Fig. 2).

Since the operation the patient has been followed closely to the present time, a period of 43 months. The menstrual periods have occurred regularly every 30 days, lasting 4 to 5 days. She had dysmenorrhea of a mild type on the first day of menstruation. Direct methods to detect ovulation have not been attempted because of the possibility of producing scarring and stenosis of so narrow a cervical canal. Papanicolaou smears taken on two occasions, July 21, 1958, and Sept. 7, 1959, revealed a luteal phase.

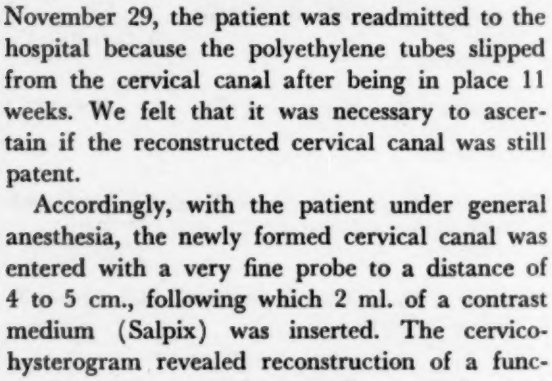

Fig. 1. Schematic drawing of surgical procedure performed. Polyethylene tubings in place appearing in the vagina.

Comment

This congenital anomaly of the cervix in the young female has been recorded in the literature eight times, excluding our case. The patients were between the ages of 16 and 25, the average age being 19 years. This age seems rather high in relation to the menarche and might be explained on the basis that these patients failed to develop hematometra or severe endometriosis and procrastinated in seeking gynecological consultation for a period of years. Another factor in this delayed investigation may be the physician's hesitation to perform vaginal examination in the young unmarried girl. This is illustrated by our case report in which the patient had noted cramps from the age of 12 but did not report for examination for 6 years. Even then she was not examined vaginally for 6 months. Active investigation of the genital tract in these cases was probably made necessary because of increased severity of the cyclic pains and continued delay of the menarche.

In this series, all of the patients underwent gynecological examination because of amenorrhea and progressive cyclic pains. In one case, that of Portes and Landrieu,[5] the pain was described as having originated only a few months previously. Since this patient was 25 years of age, this might indicate a late onset of menses.

In 6 cases the vagina was found to be normal, with no demonstrable cervix. In the remaining 3 cases, including our own, the vagina was normal but the cervix was rudimentary. In these latter cases all attempts to introduce a probe into the cervical canal were unsuccessful. It is interesting to note that in the case of Sherwood and Speed[1] microscopic examination of the ex-

cised cervical strand revealed absence of canalization.

It seems unusual that this segmental anomaly of the female occurs without any aberration in the development of the pelvic organs above or below it. Novak and Novak[8] describe this anomaly as being due to aplasia or failure of canalization of small segments of the Müllerian ducts. He further states that it results in the retention of menstrual blood after the menarche.

Actually there is little anatomical evidence that retrograde menstruation occurred in these patients. In our case, there were several blue-black areas in the left ovary which resembled small endometrial implants. Unfortunately, a biopsy specimen of these implants was not secured. In the cases of Ludwig,[2] Berard,[3] and Sherwood and Speed[1] (Table I), there is presumptive evidence of retrograde menstruation. Because of lack of reported details, however, no definite conclusions can be drawn. Ludwig noted blood in the cul-de-sac; Berard found adherence between the uterus, left ovary, and the sigmoid; and in the relatively recent case of Sherwood, there were small blue-black areas in the ovary, sigmoid, and rectum. The gross findings in these 3 cases in addition to our own are the only criteria which we felt suggested the possible occurrence of retrograde menstruation.

The fragmentary information obtained from the literature concerning operative findings, aside from the condition in the cervix and the suggestion of endometriosis, revealed that the genital organs were otherwise normal. This is substantiated by the fact that those patients who underwent plastic repair (Cases 4, 5, 6, 7, 8, and 9) (Table I) menstruated for a variable period of time following the corrective procedure. This would indicate normal function of the pituitary-ovarian axis and the capability of proper response of the end organ, the uterus.

The cervix was described as completely absent in 3 cases. In the remainder it was described as rudimentary, hypoplastic, or as a thickening of connective tissue in the midline between the uterus and vagina. In these latter cases in which a vestige of cervix was found, we believe this anomaly consisted of true atresia and not stenosis. The only positive proof of this is given by the microscopy report of the surgical specimen in Sherwood's case.

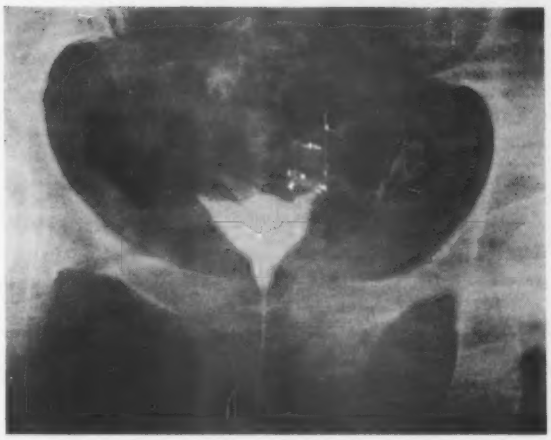

Fig. 2. Cervicohysterosalpingogram, obtained 11 weeks after operation, showing the reconstructed uterovaginal fistula. The tubes are patent. The tenaculum can be seen at bottom of the x-ray showing the level of the external os. Note the narrowness of the canal and the relative length in relation to the uterus.

Since this anomaly is rarely encountered, surgical experience is necessarily limited. However, a comparative study of the various procedures employed can be attempted (Table I).

Probably operation was performed in this group to accomplish: (1) the establishment of canalization between the uterus and vagina in order to relieve the patient's symptoms; (2) promotion of menstrual flow relieving the patient's anxiety and psychic trauma due to primary amenorrhea; (3) the creation of reproductive potentiality.

However, abdominal hysterectomy was performed in Cases 2 and 3 of Berard and Kermauner. The reasons for this are not reported. In the very first case, that of Ludwig (1900), plastic surgery was attempted, but no follow-up is available.

There are reported in the literature 5 surgically corrected cases in which the patient menstruated for at least a few months. In these cases the follow-up is incomplete,

possibly with the exception of Cases 1 and 7, those of Sherwood and Rotter, in which menstruation occurred for at least 2 years.

In all of the surgically corrected cases with follow-up, excluding our own, the principle of surgery was the creation of an anastomosis between the uterus and the vaginal vault without utilization of the rudimentary cervix. In one case the cervix was not demonstrable; in the remainder the cervix was either excised or bypassed. It is interesting to note in the case of Rotter that the cervix was bypassed because a previous surgical correction, similar to the one we employed, had failed.

In the latter case, it is understandable why the author, in view of his experience, makes the statement, "This illustrates a very important point, namely, that, if a successful result is to be achieved, the solid cervix must either be amputated or bypassed by the plastic procedure."

In our case the principle of operation was that of creating a uterovaginal fistula through the rudimentary cervix. It seems to us that our procedure might be more prone to failure as demonstrated by Rotter's first operation. Certainly it would seem that a long, narrow fistulous tract would be more prone to closure than an anastomosis in which two large openings are sutured in direct apposition to each other. However, we feel that from an anatomical standpoint our procedure is more efficacious if, besides the establishment of menstruation, future childbearing is to be considered.

We feel that uterovaginal anastomosis would predispose to abortion just as an incompetent cervix does, whereas the creation of a long fistulous tract through a rudimentary cervix would provide more normal function during the progress of a pregnancy.

No pregnancies have been reported in these corrected cases. Once pregnancy has occurred and progressed to term, elective cesarean section should be the delivery of choice. We have considered the management of abortion in the earlier months of pregnancy. The characteristic softening and imbibition of the genital organs might create conditions favorable for dilatation and curettage in our case. However, the possibility of resorting to hysterotomy through the abdominal route should be considered.

Summary

This report reviews the literature on congenital atresia of the cervix with otherwise normally developed pelvic organs and without hematometra. Another case has been presented, with particular stress on its surgical management in comparison with the other reported cases. It is concluded that the formation of a uterovaginal fistula through a rudimentary cervix should be the method of choice as a primary procedure. However, this entity is so rare and experience so limited that individualization is necessary in these cases.

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Supernumerary ovary

A case report

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THE subject of supernumerary ovary was recently reviewed in excellent detail by Wharton[1] together with case presentations. He has added 2 cases to the existing 2 supernumerary and 18 accessory ovary case reports in the world literature since 1861. He has stated concisely the definitions of these terms. In the light of this rare incidence our case must be reported.

Mrs. P. P., para i, gravida i, had been under observation for 8 years. She had one normal delivery in 1950. In 1952 a laparotomy with bilateral salpingectomy and appendectomy was performed because of bilateral chronic pyosalpinx. In subsequent years she developed severe dysmenorrhea, dyspareunia, and dysuria which led to a total hysterectomy and bilateral oophorectomy in April, 1958, with histologic confirmation of the diagnosis of adenomyosis uteri and bilateral endometriosis of both ovaries. There was no evidence at that time of any other pathologic condition.

Following the second operation, the gynecologic history was unremarkable until Feb. 24, 1960, when the patient was admitted to the hospital with excruciating pelvic pain.

Examination revealed a tender, fixed 6 cm. pelvic mass just to the left of midline. Barium enema and intravenous pyelogram revealed negative findings. Preoperative diagnosis was retroperitoneal tumor—possible sarcoma with hemorrhage. The laparotomy demonstrated a hemorrhagic 6 cm. retroperitoneal mass at the pelvic brim between the ureter and the rectosigmoid, displacing the bowel to the right. This mass was made up largely of clot and a smooth, well-encapsulated node measuring 2 by 1.4 by 1.2 cm., which was assumed to be a metastatic lymph node. A careful search of the abdomen and pelvis failed to reveal any other "nodes." Pathologic study showed: "Ovarian tissue in which there is a cyst lined by corpus luteum cells and containing some hemorrhage. The other pieces of tissue appear partly to be organizing hemorrhage and fibrous tissue and there are some portions of ovarian tissue containing follicle type cysts and also some cysts that appear to be lined by endometrial type of gland epithelium

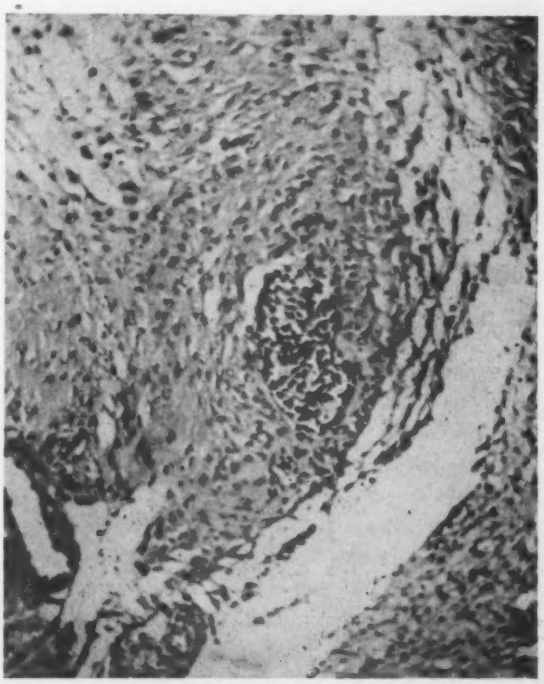

Fig. 1. Photomicrograph of a rudimentary follicle. (Original magnification ×100.)

From the Department of Obstetrics and Gynecology, Mercy Hospital.

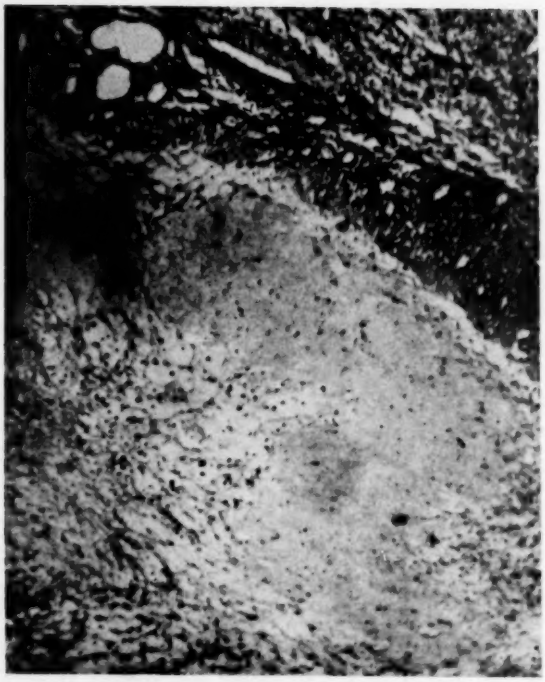

Fig. 2. A corpus albicans from the supernumerary ovary. (Original magnification ×100.)

and these also appear to have hemosiderin pigment in their walls" (Figs. 1 and 2).

Comment

The case presents several interesting considerations. First, this ovary was apparently of very little value from the standpoint of estrogen production. After the first operation (total hysterectomy and bilateral oophorectomy), she had marked vasomotor instability manifest by hot flashes, sweats, and insomnia. This was relieved by the administration of conjugated estrogens, 1.25 mg. q.h.s. There has been no appreciable change in this requirement since removal of the supernumerary ovary. Second, there had been no episodes of pain, nor was there any histologic evidence of any other corpus luteum activity in this anomalous ovary in the intervening years. Third, the genesis of the multiple microscopic areas of endometriosis just as there had been in the "sister ovaries" gives cause for speculation without conclusion.

The true nature of this supernumerary ovary, as in other reported cases, was completely unsuspected, missed in the preoperative differential diagnosis, and identified only after pathologic study.

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Femoral nerve impairment subsequent to hysterectomy

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FEMORAL nerve impairment at the time of pelvic operation is a rare lesion, if one is to judge by the sparsity of reports in the medical literature. The occurrence of 3 such cases in a short period of time, during the spring of 1954, led to the following investigation. Consultations with gynecologists, neurologists, neurosurgeons, and orthopedic surgeons disclosed little awareness of this complication. More extensive inquiry led to the discovery of 9 similar cases in the metropolitan area. These will be tabulated below.

Historical background

Pollok[1] states that femoral nerve palsies are rarely produced by gynecologic disease. He mentions that such a lesion has been reported following gynecologic operations as the result of trauma and postoperative adhesions. Mendal and Wolff[2] have reviewed 3 previously reported cases of femoral nerve paresis subsequent to gynecologic operation[3, 4] and to these have added a fourth case of their own. Recently Winlselman[5] and Johnson and Montgomery[6] have reported the occurrence of femoral nerve paralysis following pelvic operation. Postanesthetic paralysis is not infrequent and may affect various nerves. Paralysis of the femoral nerve alone or in combination with the obturator nerve may follow operative procedures in which the lower extremities are held in a position of outward rotation, abduction, and extreme flexion.

Neuritis affecting isolated nerves, if it follows surgical operation, is the result of ischemia secondary to either compression or traction.[7, 8] Slocum and associates[7] describe 4 degrees of injury as the result of such a process: (1) no effect; (2) paralysis with rapid recovery on release of pressure; (3) paralysis with delayed recovery without degeneration; and (4) complete anatomic lesion with degenerative phenomena. The first and third cases in our report belong to the third group and the second case to the fourth group.

Case reports

Case 1. Mrs. G. W., a 46-year-old white married nullipara, was admitted to the hospital because of prolonged profuse uterine bleeding and a resultant secondary anemia. She received 1,500 c.c. of whole blood during the next 3 days. On the fourth hospital day, a curettage and total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed for multiple myomas and adenomyosis. The operation was performed through a transverse, muscle-retracting, suprasymphysial incision of the Pfannenstiel type under thiopental, nitrous oxide, and cyclopropane anesthesia. A self-retaining retractor was employed throughout the abdominal portion of the operation. The patient complained on the second postoperative day of numbness over the anterior and medial aspects of the left thigh with an inability to extend the left leg. Through-

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out the remainder of her hospital stay, she was unable to stand unsupported because of muscle weakness in the left thigh. Subsequent examination revealed a numbness persisting over the anterior aspect of the left thigh associated with absent knee jerk and inability to extend the left leg. No specific therapy was recommended at this time. A gradual return of function was noted by the patient. When seen 3 months postoperatively she stated that she felt "85 per cent" improved. She was able to extend the left leg without demonstrable weakness. The knee jerk on this side was less active than that on the right. Reevaluation 7 months postoperatively revealed a complete return to normal of all objective findings. Six years postoperatively, she continues to show a complete recovery without sign of subjective or objective recurrence.

Case 2. Mrs. R. W., a 55-year-old white married multipara, was admitted to the hospital because of intermittent lower abdominal pain of 6 weeks' duration and the presence of uterine enlargement. Past history revealed intracavitary radium insertion for abnormal bleeding 2 years previously which was followed by "bilateral thrombophlebitis." Left nephrectomy had been performed for "cyst" one year prior to the present admission. On the fourth hospital day, a curettage and total abdominal hysterectomy with bilateral salpingo-oophorectomy were performed. The findings were radiation necrosis of the endocervix with a resultant cervical stenosis and a hematopyometra. The operation was performed through a transverse, muscle-retracting suprasymphysial incision of the Pfannenstiel type under thiopental, nitrous oxide, and cyclopropane anesthesia. A self-retaining retractor was employed throughout the abdominal portion of the operation. The patient complained of numbness in the left knee on the first postoperative day. Examination at this time revealed the knee jerk to be absent with inability to extend the left leg. Neurological and orthopedic consultations were obtained. The diagnosis of left femoral nerve paresis was made. A knee brace was obtained and the patient was discharged on the tenth postoperative day on a program of physiotherapy. Two months after operation, the knee jerk was absent. The patient noted some return of muscle power and the ability to move the patella. She was walking with the assistance of a knee brace at this time. When seen 3 months subsequent to operation, the knee jerk had not returned and the patient was unable to extend the left leg against resistance. There was atrophy of the quadriceps femoris on the affected side. Six years subsequent to injury, the patient was reported by her family physician to have some residual disability.

Case 3. Mrs. H. K., a 34-year-old white married nullipara, was admitted to the hospital complaining of prolonged menometrorrhagia which had failed to respond to a variety of treatments over the preceding 6 years including 3 curettages, right oophorectomy, and hormonal therapy. The uterus was of normal size, while there was an 8 cm. enlargement of the left ovary. Endometrial biopsy and hysterography revealed a marked hyperplasia. On the fourth hospital day, a total abdominal hysterectomy and left salpingo-oophorectomy without prior curettage was performed. The findings were a recurrent, polypoid hyperplasia of the endometrium and a multilocular follicular cyst of the left ovary. The operation was performed through a transverse, muscle-retracting, suprasymphysial incision of the Pfannenstiel type under thiopental, nitrous oxide, and cyclopropane anesthesia. A self-retaining retractor was employed throughout the operation. The patient first complained of numbness of the anterior and medial aspects of the left thigh and about the left knee on the second postoperative day. This was associated with inability to extend the left leg. Neurological and orthopedic consultations were held. The diagnosis of left femoral nerve paresis was made. A knee brace was obtained and the patient was discharged from the hospital on the ninth postoperative day under a program of physiotherapy three times a week. When examined 6 weeks later, the patient was walking without her brace. A definite quadriceps atrophy was present, the knee jerk was absent, and there was demonstrable extensor muscle weakness. Two months following operation, there was a return of the knee jerk and the patient was able to extend the left leg against resistance. Despite the fact that the patient stated that she was completely recovered when examined 10 weeks following operation, there was atrophy of the left quadriceps femoris muscle group and there was a noticeable limp present on walking. When examined 10 months postoperatively, the patient complained only of occasional paresthesia in the left thigh after exercise. There was no demonstrable motor defect and no residual quadriceps atrophy. Six years after her initial injury, she was found to have no residual disturbance save for a crampy pain in the lower leg precipitated

Table I

Case No.	*Hospital*	*Operation*	*Incision*	*Retraction*	*Side involved*	*Degree of impairment*	*Onset*
1	Roosevelt[9]	Total abdominal hysterectomy	Pfannenstiel	As in reported cases	Right	Complete motor and sensory	Immediate
2	Post-graduate[10]	Total abdominal hysterectomy; bilateral salpingo-oophorectomy	Left paramedian	Same	Right	Complete motor and sensory	24 hours
3	Bellevue[11]	Total abdominal hysterectomy; bilateral salpingo-oophorectomy	Pfannenstiel	Same	Right	Complete motor and partial sensory	48 hours
4	Bellevue[11]	Interligamentous cyst, left	Pfannenstiel	Same	Right	Partial motor and complete sensory	24 hours
5	Bellevue[11]	Myomectomy and appendectomy	Pfannenstiel	Same	Left	Partial motor and complete sensory	48 hours
6	Bellevue[11]	Total abdominal hysterectomy; left salpino-oophorectomy	Pfannenstiel	Same	Right	Sensory only	48 hours
7	Methodist[12]	Total abdominal hysterectomy; right salpingo-oophorectomy	Midline	Other fixed retraction	Right	Partial motor and sensory	5 days
8	Methodist[12]	Total abdominal hysterectomy; bilateral salpingo-oophorectomy	Pfannenstiel	As in reported cases	Left	Sensory only	3 days
9	Methodist[12]	Right oophorectomy	Pfannenstiel	Same	Right	Partial motor and sensory	48 hours

by fatigue. This was attributed to vascular disease by neurological and medical consultants.

Case 4. An exact duplicate of the cases presented here has been observed by Peightal and Crawford.[9] This case was that of a 48-year-old woman who had a history of previous myomectomy and 2 previous curettages. The patient underwent total abdominal hysterectomy at which time this same type of retractor and a Pfannenstiel incision were employed. Curettage was not undertaken at this operation. Postoperatively, the patient's recovery was uneventful except that almost immediately she complained of a feeling of numbness and weakness of the right leg. On the second postoperative day, neurological examination revealed a diminution to complete sensory loss over the right thigh to the level of the knee. All reflexes were absent and the quadriceps muscle group could not be contracted. Neurological consultants saw the patient on the third and fourth postoperative days. It was their opinion that the femoral nerve had either been sectioned or affected by pressure during the operative procedure. Physiotherapy was advised. Gradually, over a period of 2 to 2½ months, the patient recovered some ability to contract the quadriceps muscle group. At the end of 3 months of convalescence and physiotherapy, she could walk, although she "tired" easily. After 4 months, she was noted to have recovered full muscular strength; however, an impairment of the sensory modalities persisted.

A total of 9 similar cases occurring in 4 other hospitals in the metropolitan area have been observed since the 3 cases reported here. These cases are given in Table I. Detailed case reports are omitted, but these cases are remarkably similar and vary chiefly in the degree of nerve involvement. Because of its special interest and thorough study, Case 1 in the table has been summarized in the preceding Case 4.

Comment

The unusual nature of the nerve injury after hysterectomy prompted consultations and queries among specialists in related fields. We were unable to uncover any cases of femoral nerve involvement after hysterectomy. Search of the literature was begun. The occurrence of a second and third case only 3 days apart and 6 weeks after the original observation led to a search for factors common to all 3 patients.

The patient's position on the operating table was investigated. Restraining straps used during the induction of anesthesia were placed in the mid-thigh region, well below the area of injury. Lithotomy position was maintained for only a short period of time in 2 instances and one patient was at no time placed in this position. Moderate degrees of Trendelenburg position, similar to that used routinely, were employed. The anesthesia in each instance was of the inhalation type, similar agents being chosen merely by chance. The daily use of these agents without reported neurotoxic effects and the isolated character of the lesion observed would seem to exonerate anesthesia as having any etiological significance. Total abdominal hysterectomy with accompanying adnexal operation was performed. Injury to the intrapelvic portion of the femoral nerve by cutting or clamping was eliminated because of the distance of the operative field from the nerve. Complete transection of the nerve would result in immediate sensory and motor changes rather than the delayed onset of symptoms and signs as in the presented cases. Total disruption of the nerve could not be followed by such relatively rapid return of function. The pathologic lesions failed to reveal any causal relationship. There were no complications at the time of the surgical procedure.

By exclusion, one is left with 3 factors common to each of the cases discussed: (1) the use of a self-retaining retractor, (2) the transverse, muscle-retracting suprasymphysial incision of the Pfannenstiel type, and (3) the bodily constitution of the patients.

The same type of self-retaining retractor was employed in each case. This retractor is roughly circular when fully opened. It has 2 solid, curved, lateral blades which, though fixed to the body of the retractor, pivot on their long axis. Two removable blades are secured to the body of the retractor superiorly and inferiorly by means of wing-nuts. This differs from another type of automatic retractor which has totally stationary lateral blades that are fenestrated and have a deeper lateral curvature and a third variety which has a circular body with no fixed blades but rather several removable ones that may be secured to the body at any desired location by means of a wing-nut. Such fixed retraction differs from mobile re-

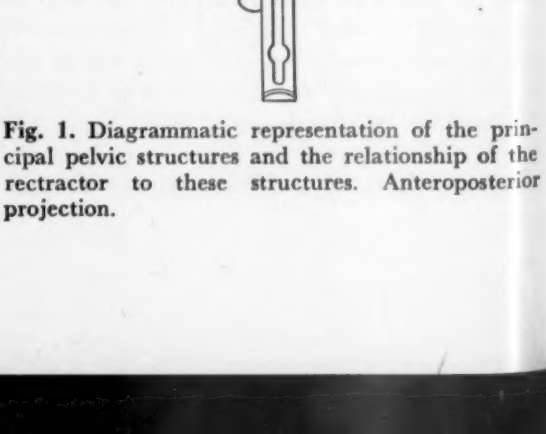

Fig. 1. Diagrammatic representation of the principal pelvic structures and the relationship of the rectractor to these structures. Anteroposterior projection.

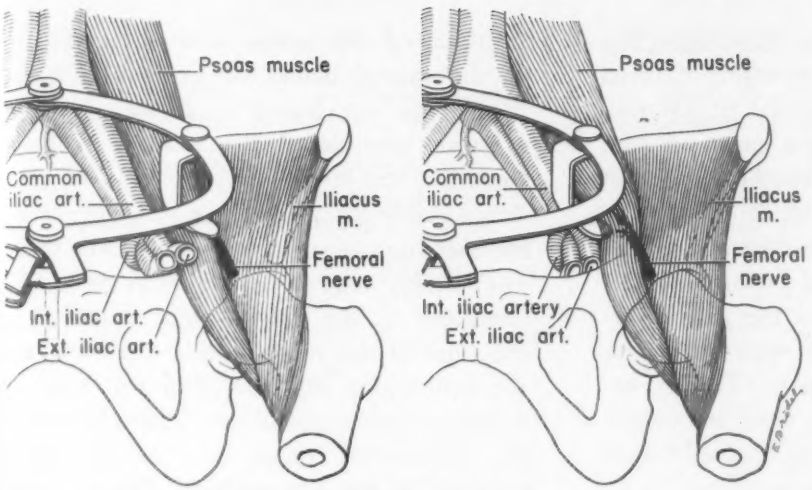

Fig. 2. Diagrammatic representation of the 2 proposed modes of injury to the femoral nerve. Anteroposterior projection.

traction since the strength of pull is constant and the duration of retraction may be longer. Pressure is then sustained and may result in ischemic necrosis of the compressed tissue. The change in location and the variation in the strength of retraction with mobile retractors obviate this difficulty.

The transverse incision permits a more lateral positioning of the lateral blades than does the midline suprapubic incision. This then increases the possibility of contact between the tip of the lateral blades and the psoas muscle and/or the femoral nerve. This concept is substantiated by the verbal report of 3 cases of sensory impairment in the distribution of the femoral nerve observed at another hospital following the use of this type of retractor in a lower midline, vertical incision.

The last consideration is that of body build. All of these patients were of average height. Two had abnormally thin abdominal walls, whereas the third was considered to have had an average abdominal wall. The thinness of the abdominal wall permits deeper and more lateral insertion of the retractor, thus further decreasing the distance between the tip of the lateral blade of the retractor and the femoral nerve. It would also seem likely that a woman with an average to small bony pelvis would be more prone to injury, since the femoral nerves are closer to the midline.

These 3 factors were investigated in the following ways. Letters to the designers, manufacturers, and distributors of this retractor failed to elicit any knowledge of such an injury.[13, 14] The retractor was placed in the abdominal incision at the time of operation on other patients and its relation to the pelvic structures noted. It was inserted in the abdominal cavity at the time of autopsy and was finally studied in a wide variety of cadavers in an anatomical laboratory (Fig. 1).

A review of the course of the femoral nerve within the bony pelvis is appropriate at this time. For a distance of approximately 5 cm. proximal to the point of entry of the nerve into the thigh, it lies in a retrofascial position in a trough formed by the lateral border of the psoas major and the anterior surface of the iliacus. It enters the thigh lateral to the femoral canal at the mid-point between the anterior superior spine of the ilium and the pubic tubercle. When the retractor was inserted at the time of postmortem examination, the femoral nerves and adjacent structures were dissected free. The relationship of these structures to each other as well as to the various parts of the retractor were studied. When the femoral nerve was isolated and the retractor placed in position, the lateral blades were seen to depress the psoas major muscle and to exert pressure on the femoral nerve approximately 4 cm. proxi-

mal to its point of entry into the thigh (Fig. 2). A second mechanism of injury demonstrated in the cadaver was that of pressure directly on the body of the psoas muscle, forcing this structure and the nerve against the lateral pelvic wall (Fig. 2). The site, duration, and strength of retraction then act to precipitate the described syndrome. The surgeon frequently visualizes the major vessels along the lateral pelvic wall but rarely encounters the femoral nerve. This is explained by the fact that the nerve is covered by a layer of dense fascia as it courses over the surface of the iliacus muscle.

The femoral nerve is made up of sensory branches which supply the middle part of the anterior thigh and the medial surface of the leg. The motor branches supply the quadriceps femoris which extends the leg, the sartorius which flexes the leg and then the thigh and rotates the thigh outward, and the pectineus and the iliopsoas which flex the thigh. Paralysis of the iliopsoas, sartorius, and pectineus muscles is evidenced by an inability to flex the thigh on the abdomen or to bring the lower trunk forward on the thigh. This was not apparent in the cases reported here, in all of which the ability to flex the thigh was retained. There was likewise no evidence of obturator nerve involvement. This nerve supplies sensory fibers to the skin of the medial portion of the upper thigh and motor fibers to the muscles of adduction. The quadriceps femoris, when paralyzed, results in an inability to extend the leg at the knee joint, a visible atrophy of the anterior thigh muscle, and an absence of the knee jerk. The clinical data localize the area of trauma to a segment of the femoral nerve distal to the origin of the branches to the pectineus and the iliopsoas muscles and proximal to the origin of the motor divisions to the quadriceps femoris muscle and the intermediate cutaneous branch which arises from the femoral nerve as it passes beneath the inguinal ligament. The actual site of femoral nerve injury must then be in a short segment of the nerve approximately 4 cm. proximal to the point where it passes beneath the inguinal ligament. Since this is the area where the tips of the lateral blades of the retractor impinge, the conclusion is inescapable that pressure necrosis of the femoral nerve is caused by the lateral blades of the retractor. A transverse incision and a thin body build increase the chance of pressure on the nerve.

The only change in operative technique instituted at the North Shore Hospital at the time of discovery of this syndrome was the prohibition of the use of this type retractor in pelvic operations. There have been no subsequent cases of femoral nerve paralysis in the intervening 6 years.

Treatment has consisted of physiotherapy to maintain muscle tone during the recovery phase and a knee brace to prevent the knee from collapsing unexpectedly under the patient. Two of these patients noted complete return of function in periods of from 7 to 10 months. The third patient was observed to have residual disability 6 years subsequent to injury.

Summary and conclusion

Three cases of femoral nerve impairment with quadriceps femoris paralysis subsequent to hysterectomy have been presented. The cause has been attributed to one type of self-retaining retractor with lateral blades which either press directly on the femoral nerve, or indirectly on the nerve, through the body of the psoas major muscle. This possibility is more likely in the presence of a transverse incision and a thin abdominal wall. Prophylaxis consists of avoiding the use of fixed retraction.

Two patients showed complete motor and sensory recovery in 7 to 10 months, while the third has residual sensory loss and interference with motor function after 6 years.

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Prolapse of a Fallopian tube after total abdominal hysterectomy

A report of one case

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IN RECENT years the literature has made us more cognizant of the diagnosis of the prolapsed Fallopian tube following hysterectomy.[1-8] This diagnosis should be entertained when a granular mass in the vaginal cuff is encountered after hysterectomy.

The patient, a 37-year-old white woman, gravida iv, para iv, was first seen in consultation because of a vaginal discharge consisting of a watery straw-colored fluid which had been occurring for one year after a total abdominal hysterectomy and right salpingectomy. She also had postcoital bleeding in recent months. Except for occasional bloating she had no other complaints.

She had received no care since the original operation, even though she had noticed this watery discharge a few weeks postoperatively. There were no details of the operative technique available. The patient stated that after the operation she developed severe abdominal distention, which resulted in intubation and a prolonged hospital stay.

Pelvic examination revealed a one inch red, granular, polypoid mass protruding from the right fornix of the vaginal vault with a nonabsorbable sutured stump of tissue just lateral to it. It was assumed that this could be a prolapsed tube. The mass bled easily. On palpation a sound was easily inserted into a lumen-like tract of the presumed tubal mass to a depth of 1¼ inches, after which it met an obstruction. Further examination revealed a soft induration around the vaginal cuff and a moderate amount of tenderness.

A vesicovaginal fistula was ruled out by means of inserting 200 c.c. of methylene blue into the bladder and observing the vaginal cuff to see if any dye would drain into the vagina. The following day a ureterovaginal fistula was ruled out by means of administering 5 c.c. of indigo carmine dye intravenously and similarly observing the vaginal cuff for drainage. Both tests were negative. An intravenous pyelogram was also done and was found to be normal, with no distortion to the ureters.

The patient was hospitalized and a laparotomy was performed on Oct. 27, 1959, for prolapsed Fallopian tube. The operation revealed a tuboovarian mass, which was soft and cystic, approximately 5 cm. in diameter in its widest portion, and completely covered with parietal peritoneum. The mass was fusiform in appearance and extended from the mid-portion of the vaginal cuff upward, along the left lateral pelvic wall of the pelvis to the infundibulopelvic ligament. The ligament was elongated about three times its normal length and was accompanied by engorged blood vessels. The hydrosalpinx, which perforated on removal, contained a yellow watery fluid in its most distended portion, whereas the more indurated part of the tube which inserted into the vaginal cuff contained a thick white fluid.

The bladder flap was attached to the anterior portion of the vaginal cuff and at no time was it necessary to disturb it in removing the mass.

Although cultures of the white discharge revealed *Escherichia coli,* the patient had an afebrile uneventful postoperative course, and no need of any type of antibiotics. Follow-up care was also uneventful and repeated pelvic examinations revealed a well-healed vaginal cuff.

Comment

In the literature there are 28 cases recorded. The cause has been attributed to postoperative hemotomas, infections, abscesses, and poor surgical technique.[5-7] Gauze packs and drains have also been suspected,[1-3, 7, 8] while vaginal hysterectomy appears to be the predominant procedure in the statistical surveys thus far presented.[2, 3, 7, 8]

A protruding granular mass from the vaginal cuff warrants a differential diagnosis which should include granulation tissue, prolapsed tube, endometriosis, benign papillomas, condyloma acuminata, prolopsed omentum, ovary, loop of bowel, and recurrent malignancy.[4-7] It should also be mentioned that with a watery type discharge the possibility of a ureterovaginal or vesicovaginal fistula must be considered.[8]

In the case presented the ovary showed signs of strangulation and might well have prolapsed along with the tube had it not been for the infundibulopelvic ligament. One wonders how much damage remains or has been done to the ovary after prolapse of the tube. It seems that it would be minimal if treated fairly soon postoperatively. It would be interesting to determine how many of these treated cases required, at a later date, operation for ovarian disease due to disturbed circulation to the ovary. In a young woman, one would think that replacing the ovary in its normal anatomical position may well preserve its function.

Therapy has consisted of simple cauterization, amputation of the prolapsed portion of the tube, and salpingectomy, vaginally or abdominally.[5-8] The procedure that has been done the least is abdominal salpingectomy. In this case it most certainly appeared to be the procedure of choice because of the hydrosalpinx and enlarged cystic ovary.

Summary

A case of prolapsed Fallopian tube after total abdominal hysterectomy has been reported.

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CURRENT OPINION

Pertinent comments

A possible seasonal effect on parturition

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IN THE course of a study of fetal mortality, the records of all births in the City of New York during 1957 to 1959 were cross-tabulated by month of occurrence and by length of gestation. A short extract from these data is given in Table I, where it will be noted that local maxima in the daily number of births occurred: during August, for infants of 34-37 weeks' gestation; during September, for infants of 38-41 weeks' gestation; during October, for infants of 42 or more weeks' gestation (Table I).

This is, of course, the type of pattern to be expected as a consequence of fluctuations in the numbers of conceptions per day, because the births of infants who were conceived at about the same time will tend to concentrate along a descending diagonal of the table. As an example, suppose that Infants A, B, and C were conceived on the same day and are respectively destined to be born at some gestational age in the ranges 34-37 weeks, 38-41 weeks, and 42+ weeks. Then, given that A is born in July, it can be calculated that there is a probability of about 0.69 that B will be born in August, and a probability of about 0.65 that C will be born in September. Other things being equal, one would therefore expect to find positive correlations among the daily rates belonging to the same descending diagonal of the tables. Despite the appearance of the extract quoted, this expectation was not fulfilled by the data referring to 1957-1959 when considered as a whole. In particular, the correlation between numbers of births per day in the 34-37 and 42+ groups was *negative* at –0.345 (based on 34 corresponding pairs of months).

Fig. 1 shows how this unexpected negative correlation arose. Births at 34-37 weeks had a marked seasonal pattern alternating between high daily rates in midsummer and low rates at the turn of the year. Births at 42+ weeks also showed seasonal alternation, but instead of following the 34-37 week group with the expected lag of about 2 months, these later births had their seasonal peak just after the seasonal minimum of the

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Table I. Average daily number of births

Month of delivery	*Completed weeks of gestation*		
	34-37	*38-41*	*42+*
July	65.83		
August	69.16	320.90	
September	62.80	349.43	52.77
October		327.81	53.71
November			48.57

early group. The intervening group of births near term showed high daily rates in each September, but over the year as a whole its variation was proportionately very much smaller and less regular than that of the earlier and later groups. Deliveries in the interval 30-33 weeks had no perceptible seasonal pattern. Taken together, these findings imply that there is some tendency for births due in the summer to occur before term and for those due in the winter to be relatively delayed.

A rough index of the tendency toward early delivery among infants due in a given month (say, August) may be obtained by subtracting the daily number of 42+ births in the following month (September) from the daily number of 34-37 births in the preceding month (July). Thirty-four such differences have been plotted in Fig. 2, where it will be seen that the variation of this index is unmistakably periodic and can be closely fitted ($r = 0.924$) by a sine curve. On partitioning the variance of the index between the 3 degrees of freedom associated with the fitted curve and the 30 associated with residual variation, an F ratio of 59.15 was obtained, which is more than eight times the value required to establish significance at the 1 in 1,000 level.

The effect of this variation on the average length of gestation cannot be estimated with any precision from the present coarsely grouped data, but probably amounts to a difference of 1 or 2 days between the seasonal extremes. To put it another way: fetuses entering the thirty-fifth week of gestation in July appeared to incur a risk of delivery of 2 or more weeks before term of 0.154, compared with 0.131 for those reaching the same stage in January.

Comment

Before concluding that there is evidence of a genuine seasonal effect on parturition, attention must be given to other possible explanations.

An effect of the type found might have arisen spuriously if errors in the classification by length of gestation had a gross seasonal bias. Since this classification depends ultimately on the mothers' statements regarding the date of the last menstrual period, such an explanation would require that periods were especially likely to be missed—other than on account of a continued pregnancy—in the spring. Alternatively, or in addition, periods might be especially likely to persist after a conception occurring in the fall.

It is likely that the women going to term in summer and winter months differ slightly in age—and parity—distribution, but this could not explain the present observations for, according to Gibson and McKeown,[1] there is no consistent relationship between length of gestation and either maternal age or parity.

Births to women resident outside New York City may differ from others both in respect of seasonal distribution and length

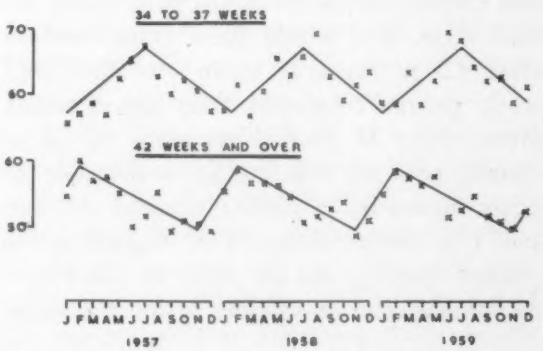

Fig. 1. Seasonal alternation of births per day in two ranges of gestational age, New York City, each month of 1957-1959.

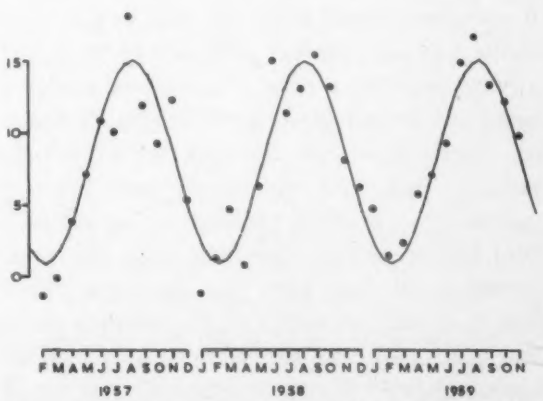

Fig. 2. Index of tendency to early parturition (see text) and fitted sine curve, New York City, February, 1957, to November, 1959.

of gestation, but as these constitute only about 5 per cent of all births occurring in the city they could not be responsible for more than a small fraction of the fluctuation shown in Fig. 2.

If the apparent seasonal variation in date of delivery is genuine, it could still be an artefact in the sense that resort to induction before term might be more common in summer than in winter. Some support for this interpretation can be derived from the study by Clyman and associates[2] relating to the use of oxytocin in New York City during 1955 and 1956. According to these authors, in about 5.4 per cent of live births in July, compared with 3.9 per cent in January, labor had been induced by oxytocin. This difference is in the direction consistent with the present findings but is much too small to account for them in full. For even if one assumed that *every* "extra" induction in July was carried out a minimum of 2 weeks before term, this would have transferred at most 1.5 per cent of births into the 34-37 week group, compared with the estimate given above of over 2 per cent. (It is, of course, possible that induction of labor by other means has a similar seasonal distribution.) A further difficulty in explaining the present findings on the basis of the report by Clyman and co-workers is that the single month with the highest frequency of births induced by oxytocin in both 1955 and 1956 was December, yet, according to Fig. 2 this month had no net excess of early deliveries in 1957 or 1958.

Summary

Births in New York City during 1957-1959 exhibited a slight but regular tendency toward earlier delivery in the summer than in the winter months. No fully satisfactory explanation of this phenomenon has been found, but it may be due in part to seasonal variation in the use of oxytocin to induce labor before term.

I wish to acknowledge the aid of Dr. Morris Siegel of the Downstate Medical Center and the cooperation of staff of the Bureau of Records and Statistics, Health Department of the City of New York. I am indebted to Dr. M. H. Rand for pointing out the optimal fitting procedure of use of a sine wave to periodic data.

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Position of women in childbirth

A study in data quality control

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THIS is a study of the position of women during parturition in 76 non-European societies, mostly primitive tribes. The research was stimulated by Howard's obstetrical theory[7-11]; Howard maintains that the upright position is advantageous in that it reduces the period of labor and the need to use forceps, because in the upright position the direction of gravity and the direction of the expulsive force are synergized. Howard supports his thesis by a number of arguments as well as by clinical data. This paper focuses on one of the arguments used by Howard—that the supine position in general use by modern Western physicians is abnormal and unphysiologic. We here examine the evidence for the thesis that in most non-Western societies woman in childbirth is in fact usually in an upright position.

This study is a systematic review of evidence on childbirth in the Human Relations Area Files. These files are a collection of hundreds of firsthand reports about a large sample of human societies from all over the world; the files are so arranged that the original text of any passage which deals with childbirth in any of the reports in the file can be quickly located and consulted.[12, 13] An earlier survey by Ford[4] in a precursor of these files had already reported that most of the peoples in the sample used the upright position in childbirth. The purpose of the present study is to examine similar evidence critically, in order to assess the reliability of Ford's findings. This task is necessary because so few of the reports on childbirth among non-Western people are eyewitness accounts; almost all are hearsay.

In classifying reports of childbirth, the problem has often been to interpret positions of women as described by field workers in order to see whether they fell into Howard's physiologic category or not. The basic concept we have used in this thinking is that of the *upright* position. We think of an upright position as one in which a line connecting the centers of the woman's third and fifth lumbar vertebrae is more nearly vertical than horizontal, and furthermore is so in such a way that the third lumbar vertebra is higher than the fifth, rather than vice versa. When a woman is in such a position, gravity assists childbirth by tending to pull the head of the infant through the birth canal. In practice, we commonly find four distinct varieties of the upright position: (1) sitting, in which a woman rests chiefly on her buttocks, although she may also lean against some support[11]; (2) squatting, in which her weight rests chiefly on her feet, but her knees are markedly bent; (3) upright kneeling, in which her weight is chiefly on her knees; and (4) standing, in which her weight

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is chiefly on her feet and her knees are bent slightly or not at all.

In contrast to the *upright* position in any of its variant forms, we have what we call the *neutral* position. By a neutral position, we mean simply one in which the requirements for the upright position are not met, and consequently in which gravity does not significantly assist childbirth by tending to pull the head of the infant through the birth canal. In practice, three variant forms of the neutral position occur: (1) the supine position, that generally used in modern Western obstetrics, in which the weight of the woman rests chiefly on her back; (2) the prone position, in which she lies on her stomach; and (3) the quadruped position, in which a woman squats or kneels with a large part of her weight supported by her hands or elbows. We do not know of any actual examples of the other theoretically possible neutral position: inverted, in which the fifth lumbar vertebra is substantially higher than the third (which would almost require the woman to stand on her head) and mention it only to complete our survey of the theoretical possibilities. Rarely if ever does a woman maintain herself in the upright position without some kind of support. No less than 32 of the peoples in our sample provide the parturient with some kind of mechanical support to help maintain an upright position; some peoples drive stakes into the ground or the floor for her to hold on to, others have her hang onto a rope suspended from the ceiling or rafters, or lean against a post or wall. Almost always, the parturient is attended by helpers, usually one or more female relatives who act as midwives. Very commonly such a helper physically supports the parturient, often holding her in the midwife's lap, or grasping her from behind.

While our study definitely shows an overwhelming preference for some kind of upright position among peoples outside Eurasia, no one upright position can be singled out as the "normal" or "natural" one. In parturition positions, as in so many other traits, primitive peoples display a wider variety of culture patterns than civilized peoples. Of the 62 peoples using upright positions, 21 use some kind of kneeling position, 15 use some kind of squatting position, 5 use a standing position, and 19 use a sitting position. Most of the neutral reports simply describe the parturient as lying down, without saying whether she is prone or supine; but the Hottentot are specifically reported to assume a prone position, and the Bontok on occasion to take a quadruped position.

While the general nature of human culture tends to make childbirth like other activities follow the locally approved pattern, variations do sometimes occur. To begin with, one position may be that used by most women throughout labor (let us call that the *normal* position), while another position may be used by a lesser proportion of women in the same society, for example, by women whose labor is unusually prolonged or difficult. Second, the culture pattern may dictate one position through the earlier stages of labor and another position through the later stages; let us here call the position taken by a woman during most of the time she is in labor the *usual* position. In this study, we are chiefly interested in what we call the usual-normal (UN) position, the position taken by most parturients in a given society for the greater part of the time of childbirth (Table I).

Our study solidly confirms Ford's findings and clearly establishes that some upright position is followed among most non-European peoples—especially outside Asia. Of the 76 societies in which a parturition position was reported with sufficient clarity for us to be able to make an inference, 62 used some kind of upright position and only 20 some kind of neutral position. Furthermore, 9 of these 14 were found among the 28 peoples in this sample from Asia and North Africa. Among the 48 peoples from the rest of the world, only 5 were reported to use a neutral position.

The main emphasis of this study is the critical analysis of this finding to test the hypothesis that it is an artifact of errors in the research process. The method we use is called data quality control. This is a method

of systematic study of the data collection process to search for evidence of error—a method developed by Naroll.[16, 17] In studies of library reports, the conditions of data collection cannot be controlled before the observations are made as they are in laboratory research. Data quality control cannot prevent error in observation—but it can detect it.

Errors in the research process need to be classified into two major types, random error and bias. Furthermore, the ethnological research process itself needs to be classified into three stages of data collection: informant's observations, ethnographer's observations, and comparativist's observations.

As to the first of these classes, random error is defined as error which proceeds from circumstances which are equally likely to affect the final result in either direction. In the present study, a random error is an error which results from a circumstance which is as likely to cause an upright position to be reported as a neutral one as it is to cause a neutral position to be reported as an upright one—no more likely, no less likely. A bias, on the other hand, is an error which tends systematically to favor one result over the other. In the present study, a bias is a circumstance which tends to affect one kind of report on parturition position more than the other. For example, if the comparativists (i.e., the authors of the paper) tended systematically to treat doubtful or ambiguous reports as reports of upright deliveries, that would constitute a bias. If informants tended systematically to report neutral (European style) deliveries because they are the "modern" way, even though in fact deliveries were usually upright, that would constitute a bias. Any circumstance, whether deliberate or accidental, which systematically favors a particular outcome of the study by producing reporting errors in a consistent direction is a bias.

As to the stages in the ethnological research process, one must keep in mind the manner in which the information here relied on was collected. Most of the reports on parturition position were made by ethnographers (almost all professional anthropologists, missionaries, or government officials) who had not themselves actually witnessed delivery. The ethnographer gets his information on this as on so much else by systematically questioning informants. An ethnographer investigates culture patterns—regular, repetitive ways of life. Most American middle-class urban women give birth lying on an operating table attended by a professional physician and his professional assistants—this is a repetitive culture pattern. We are interested in this paper in the corresponding patterns of other societies with other cultures. The usual way for an ethnographer to learn the details of patterns he cannot witness himself is by working with informants. A good ethnographer chooses a rather small number of informants, of the order of half a dozen. With these people, he forms close, intimate relationships. Systematically, he talks with them, week after week, month after month. He takes copious notes, on the spot at the moment if he can. He checks an informant's statements today against those he made last week or last month. He checks one informant's statements against those of another. And he checks informants' generalizations against detailed case histories which he elicits from them.

Most of the data on childbirth was collected by field workers more or less following this general approach. Few of them were specially interested in childbirth practices; most of the reports we have simply come from the ethnographer's frequent practice of trying to record everything that seems important about the way of life of the people he studies.

First stage of observation: the informant

The first stage of this data collection process then is usually the informant's observations. The most likely informant on childbirth is an elderly woman. Elderly people are very often the best informants because in the first place they know the most

Table I. Position reports*

People	*Position report*	*Favorable observation conditions*	*OQI*	*Observer*
Negro Africa				
Ashanti (1921)	UE	S, C, L	U 3	Rattray
Azande (before 1911)	NS		U 4	Anderson
Azande (1915)	UE	L		Colonne-Beaufaict
Azande (ca. 1920)	UE	S, L		Larkin
Bemba (1934)	UE	F, S, L	U 4	Richards
Ganda (1932)	UE	F, L	U 7	Mair
Ganda (ca. 1900)	UE	S, L		Roscoe
Hottentot (1905)	NE	S, L	N 3	Schultze
Luo (ca. 1920)	UE	L	U 2	Hartmann
Mbundu (ca. 1930)	US	S, L	U 2	Childs
Nuer (before 1931)	UE	F, S, L	U 4	Huffman
Nyakyusa (ca. 1925)	UE	F, S, L	U 0	Mackenzie
Nyakyusa (1938)	NS	F, S, L		Wilson
Tanala (1927)	UE		U 1	Linton
Thonga (1926)	US	S, L	U 2	Junod
Tiv (1952)	UE	F, S, L	U 13	Bohannon
Tiv (1932)	UE	S, L		Downes
Tiv (ca. 1925)	UE	S, L		East
Asia and North Africa				
Afghan (1940)	NE	F, S, L	N 4	Hackin
Amharic (1954)	US	L	U 1	Messing
Andamans (ca. 1880)	UE	S, L	U 7	Man
Andamans (1908)	UE	S, L		Radcliffe-Brown
Burusho (1924)	US	F, S, L	U 1	Lorimer
Cambodian (ca. 1930)	NS	F	N 2	Poree and Maspero
Chamar (before 1920)	UE		U 1	Briggs
Gilyak (1905)	UE	I	U 2	Pilsudski
Hadhramaut (before 1932)	US		U 0	Thomas
Hausa (1950)	NE	F, S, C, L	N 4	Smith
Inner Mongolian (before 1938)	UE	S, L	U 3	Kler
Iranian (ca. 1923)	UE	L	U 2	Masse
Jordanian (ca. 1930)	UE	F, S, C, L	U 4	Granqvist
Kamchadal (1740)	UE	S, C	U 2	Krasheninnikov
Korean (1947)	NE	I	N 2	Osgood
Laotian (before 1952)	UE		U 3	Deydier
Laotian (ca. 1900)	UE			Reinach
Lepcha (1937)	UE	C, L	U 5	Gorer
Lepcha (1937)	UE	L		Morris
Manchat (before 1932)	NE	E, S, I, X	N 2	Asboe
Manchurian (1918)	UE	F, S, L	U 4	Shirokogoroff
Miao (ca. 1895)	UE		U 6	Diguet
Miao (ca. 1930)	UE	F, S, L		Graham
Moi (before 1936)	NE		N 1	Morizon
Monguor (ca. 1915)	NE	S, L	N 3	Schram
Rif (1928)	UE	F	U 2	Coon
Rwala (ca. 1908)	UE	C, L, X	U 1	Musil
Semang (ca. 1930)	UE	L	U 5	Evans
Semang (1925)	UE	L		Schebesta
Thailand (1949)	NE	S	N 5	De Young
Thailand (ca. 1910)	NE	S		Graham
Toda (1902)	UE	L	U 2	Rivers
Vietnamese (1951)	NE	E, S, I, L	N 7	Dê
Vietnamese (before 1880)	NE	S		Landes
Yao (ca. 1895)	UE		U 2	Diguet
Oceania				
Apayao (ca. 1930)	US	S, L	U 2	Vanoverbergh
Aranda (ca. 1918)	UE	X	U 2	Basedow

Table I—Cont'd

People	*Position report*	*Favorable observation conditions*	*OQI*	*Observer*
Aranda (1946)	UE	I		De Vidas
Aranda (1929)	NS	S, L		Roheim
Ifugao (1937)	UE	S, C, L, X	U 5	Barton
Ifugao (before 1941)	UE	L		Lambrecht
Kapauku (1955)	US	L	U 1	Pospisil
Kurtatchi (Buka) (1930)	UE	E, F, S, I, L, X	U 4	Blackwood
Lau (1934)	UEL	F, L	U 3	Thompson
Maori (before 1929)	UE		U 5	Best
Maori (before 1950)	UE	S, L		Buck
Pukapuka (1935)	UE	E, F, S, L	U 5	Beaglehole
Trobriands (ca. 1920)	UE	S, L	U 3	Malinowski
Wogeo (1934)	US	I	U 1	Hogbin
Woleai (1903)	UE		U 3	Born
Woleai (1948)	UE			Spiro
North America				
Comanche (1933)	NE		N 1	Wallace and Hoebel
Copper Eskimo (ca. 1900)	UE	L	U 2	Rasmussen
Crow (ca. 1915)	UE	L	U 2	Lowie
Krangmalit (before 1955)	UE	E, S, L, X	U 3	Coccola and King
Nahane (1945)	UE	F	U 6	Honigmann
Nahane (1915)	UE	S, L		Teit
Navajo (1942)	UE	F, S, C, L	U 15	Bailey
Navajo (before 1944)	UE	F, S, X		Leighton and Leighton
Navajo (before 1939)	UE	I		Lockett
Navajo (1925)	UE	F, S, L		Reichard
Northern Paiute (ca. 1930)	UE	F	U 4	Kelly
Northern Paiute (ca. 1912)	UE			Lowie
Papago (1935)	UE	F, S, L	U 4	Underhill
Southern Ojibwa (1939)	UE	F, S, C	U 3	Hilger
Southeast Salish (1930)	UE		U 1	Ray
Tlingit (ca. 1900)	US	S, L	U 2	Jones
Tubatulabal (1933)	UE	F, L	U 3	Voegelin
Yurok (ca. 1939)	NE		N 3	Erickson
Yurok (ca. 1920)	NE			Kroeber
South America				
Araucanians (1952)	US	F	U 3	Hilger
Araucanians (1948)	US	F		Titiev
Aymaran (1942)	UE		U 1	Tschopik
Bororo (1939)	US		U 1	Oberg
Callinago (ca. 1937)	UE	L	U 2	Taylor
Cariban (1933)	US	L	U 1	Gillen
Cayapa (1909)	UE	L	U 2	Barrett
Cuna (1947)	NE		N 1	De Smidt
Jivaro (1908)	UE		U 5	Rivet
Jivaro (1931)	UE			Stirling
Jivaro (before 1930)	UE			Tessman
Mataco (1939)	UE		U 1	Metraux
Nambicuara (1939)	UE		U 3	Levi-Strauss
Nambicuara (1949)	UE			Oberg
Siriono (1941)	NE	E, L	N 3	Holmberg
Tupinamba (1613)	UE	S, L	U 3	Evreux

*Key: Column 2: UE, upright explicit; US, upright suggested; NE, neutral explicit; NS, neutral suggested. Column 3: E, eyewitness; F, female observer; S, stay over one year; I, special interest in parturition; C, case account by informant; L, native language familiarity; X, example only reported. Column 4: U, upright; N, neutral.

about their culture and in the second place they have abundant leisure and enjoy talking. An elderly woman in nearly all the societies studied is likely to have given birth many times herself and to have assisted personally at the delivery of many of her relatives. Childbirth is relatively more frequent among non-Western societies than in the West; contraception is less often and less effectively practiced; the infant mortality rate is very high (often of the order of 50 per cent) and so for the society to reproduce itself most women need to bear 5 or 6 children. Consequently, informants in non-Western societies are likely to know much more about parturition practices in their societies than nonprofessionals would know in ours.

Let us, however, consider the possible sources of informants' errors. We define an informant error as a circumstance which leads an informant to form an erroneous mental image, or memory, of an event or a culture pattern. (Where an informant has an accurate mental image but for reasons of his own makes a misleading report to an ethnographer, we class this as a second stage error, an ethnographer's error.) Three main sources of informant error occur. Perhaps the most common is the distorting influence of a cultural theory or stereotype. A citizen of a large American city, for example, might report that its mayor is chosen by popular election—he is supposed to be, and in fact elections are regularly held as scheduled. A foreign ethnographer, however, might in some cities consider the elections mere ceremonial ratifications of the choice of a political boss. There are two well-known primitive societies, the Arunta and the Trobriands, where the people deny that there is a causal relationship between sexual intercourse and pregnancy; in both these societies, the cultural value system has another theory of pregnancy which is central to the people's ideology. So informants can form false mental images of patterns in their own culture because they are misled by their culture's theory of itself.

A second possible source of informant error might arise from a poor choice of informant by the ethnographer. Should the ethnographer question an informant about a subculture pattern with which the informant is not familiar, he might report his erroneous impressions of that activity. Men might not know much about childbirth in societies where only women are supposed to be present at the parturition scene.

A third possible source of informant error might arise from faulty memory of the details of a particular unique event. Historians, overwhelmingly concerned as a rule with the reconstruction of the details of unique events, are understandably skeptical of the accuracy of memoirs in which participants describe past events from memory. Should an informant have participated in only a single childbirth, either as principal or as attendant, he might well make such an error. On the other hand, we submit that this kind of error is not likely to be made about repetitive patterns, events which take place over and over again according to a culturally dictated program.

Second stage of observation: the ethnographer

Where an ethnographer personally witnesses an event or a practice, the first stage of observation is directly checked (but even then, often the ethnographer relies on the informant for assurance that the event witnessed is a typical example of a recurrent pattern). Six of the 104 reports are eyewitness accounts by an ethnographer who was present at a childbirth. This is, of course, the most reliable kind of observation: the ethnographer is free of the theoretical bias of the culture studied and by taking notes at the time frees himself from dependence on his own faulty memory.

The major source of second stage error arises out of the dependence of ethnographers upon informants. Informants may lack candor. They may be unwilling either to answer a question truthfully or to decline to answer and may instead deliberately tell an untruth. There are many circumstances in which this is likely to happen. In some societies, people tend to give the answer

they think the questioner wishes, simply to please him—this is considered common courtesy. In our society, we are likely to do this when questioned by a woman about the attractiveness of her clothes.

Or often the informant may have, or may think he has, some benefit to be gained by misleading the foreign stranger. He may deny any belief in witchcraft when in fact he is terrified of sorcery because he does not want to seem knowledgeable on that subject, for fear of being thought a witch himself. He may conceal the size of his family or the resources, from a census taker because he thinks (perhaps correctly) that he will thus lower his burden of taxes or forced labor. He may simply be embarrassed to give a correct answer. In our society, questions about sex relations and personal income often produce intense embarrassment. In some societies, childbirth is considered a highly personal, private function, embarrassing to discuss with a stranger. Another common source of embarrassment may be self-consciousness about culture practices which the informant himself has begun to think of as "backward" or "primitive" because non-European. Since Europeans regularly give birth in a supine position, it is plausible to suppose that some informants might be tempted to mislead ethnographers by erroneously reporting the use of such a position among their people, simply in order to make them seem more "modern."

Another source of second stage bias might be the theoretical orientation of a field worker, which might lead him to notice and report events and patterns which support a particular theory (Marxism, functionalism, capitalism, Freudianism) but to overlook and fail to report events and patterns which are inconsistent with such a theory. This study contains no control for this bias, simply because we know of no theory involving parturition among primitive people except Howard's own, which evidently was unknown to all of the authors of the reports used here (practically all of which were published before Howard's first paper on the physiologic position).[8]

Third stage of observation: the comparativist

By the comparativist in a study like the present is meant the person doing the research, the person reading the ethnographer's field reports and compiling statistics from them. Theoretically, a comparativist might deliberately falsify his reports. In many comparative studies, comparativists systematically cull evidence which favors their thesis and ignore evidence which favors the contrary thesis; this is the method used by forensic speakers and attorneys. Finally, a comparativist may tend to interpret vague or imprecise reports in a manner which favors the comparativist's thesis, like a baseball umpire who calls all the close ones in favor of the home team.

The controls

The present study offers controls both for bias at each of the three stages of observation and for random error. These controls involve contrasting reports known to have been made under presumably better conditions of observation with those not so known. Wherever no information has come to hand about a given condition of observation, we have treated the report as made under the presumably poorer condition. Undoubtedly, many of the reports listed in Table I actually were made under better conditions than there shown; for example, Best is generally accepted as a leading authority on the Maori and so we would presume lived for years among them, spoke Maori fluently, and for all we know may have witnessed several childbirths; but he fails to report any of these observation advantages in the work we consulted and so no evidence has come to hand to permit us to credit him with any of these advantages. Time did not permit us to search for further information on observation conditions; we used only that at hand.

Random error

In a study like the present, random error if sufficiently prevalent would most likely produce a conclusion that the two

methods are practiced with about equal frequency. This follows whether in fact they are so, or whether in fact one method is practiced much more than the other. For if they are in fact practiced with about equal frequency, random error would be likely to change an "upright" report to a "neutral" report about as often as vice versa, leaving the final statistical result the same. But if one method—say the upright, for example—were in fact more widely practiced, random error would be more likely to change an upright report to a neutral report than vice versa and so tend to even them out.

Since we find about 80 per cent of the societies reportedly upright in parturition positions, a suspicion that random error has influenced these reports can only lead us to suppose that the true disparity is even greater!

However, we have a check for random error, which leads us to conclude that it is a comparatively unimportant factor. On 23 of the 76 reports, we have more than one independent report. Of these situations where one ethnographer has in effect checked the work of another, 20, or 87 per cent, produce corroborative reports while only 3, or 13 per cent, produce conflicting reports. Independent checking does not guard against bias, as a rule (though it does provide a guard against the personal bias of the ethnographer) but does guard against random error.

First stage bias

We have two quality control tests on first stage bias (Table II). First there are 6 eyewitness accounts by ethnographers. Three of these report upright deliveries; 3 others, neutral. This is a high proportion of neutral reports, considering the fact that less than 20 per cent of all reports are neutral. However, Fisher's Exact Test shows that 17 per cent of the time we would expect this extreme a result from random samples of a population in which the true proportion of neutral deliveries is as we here report it. Consequently, we dismiss this result as merely reflecting a freak of sampling, especially since all the other quality control tests are much more favorable to us. After all, if as here we conduct 9 formal tests on a sample, we would expect one of them at least to turn out this badly by mere chance (Table II).

Our second quality control test on first stage bias does not offer any further support to the hypothesis that informants tend to misunderstand parturition position of their society. This test looks at the reports in which informants relate a specific childbirth instance—in which they make a case report. For example, so-and-so gave birth to her first child in such-and-such a position. A report of this sort is less likely than a generalization to be influenced by an erroneous cultural stereotype, since attention is now focused on a particular event in which the informant presumably took part. We have 8 such reports in this sample; 7 of them report upright deliveries. This is a higher proportion of upright reports than that among generalizations. If the true proportion of parturition positions were half and half—half upright, half neutral—the cumulative binomial probability distribution[5] shows that we would expect so extreme a result in less than 8 per cent of random samples.

Second stage bias

We have 3 quality control tests which check second stage bias. All of these measure indirectly the degree of rapport which the ethnographer is likely to have with his informants. The better his rapport, the less likely his informants are to deceive him. All competent ethnologists are keenly aware of the dangers of second stage error. They seek to reassure their informants by promising to keep all information confidential—and by keeping this promise faithfully. They seek to gain their personal confidence and friendship. They avoid leading questions until they are assured that informants do not follow—or have learned to cease following—the practice of answering questions in the way they think the ethnographer wishes. A good ethnographer trains his informants to take skilled part in the ethnographic data

Table II. Data quality control tests

Control factor	*Factor favorable*		*Factor unfavorable*		*P**	*Statistical test used†*
	Upright positions reported	*Neutral positions reported*	*Upright positions reported*	*Neutral positions reported*		
First stage bias						
Eyewitness	3	3	81	17	**0.17**	A
Informant case report	7	1	77	19	1.0	A
Second stage bias						
Ethnographer's sex	23	4	61	16	*0.50*	B
Length of stay in field	38	11	46	9	**0.28**	B
Familiarity with native language	51	8	33	12	*0.09*	B
Third stage bias						
Report explicitness	79	17	5	3	1.0	A
Report generality	79	19	5	1	1.0	A
Whole process						
Observation quality index (OQI)	—	—	—	—	**0.95**	C

*In this column is entered the probability of obtaining a result this unusual in either direction by random sampling from a universe in which there is in fact no report bias. Probability entries in boldface type show results tending to indicate a bias in favor of upright positions; those in italic type show results tending to indicate a bias in favor of neutral positions; those in roman type show results tending to indicate no bias in either direction.

†Key to symbols: A, Fisher's exact test; B, chi square test; C, Mann-Whitney "U" test.

collection work. But this takes time. And it takes sufficient familiarity with the native language to dispense with the services of interpreters where necessary and to check their work where used. Familiarity with the native language has many other advantages in field work,[14] so much so that British anthropologists today feel it is an indispensable requirement. A third factor importantly affecting rapport where the study of childbirth is concerned is the sex of the ethnographer. Childbirth of course always involves the intimate affairs of women. In many societies, it is not men's business, and men ordinarily take no part in it. But it generally is a topic which women often discuss among themselves. Presumably, then, a woman ethnographer is likely to have better rapport with women informants and hence less likely to be misled through informants' embarrassment.

All 3 second stage tests are reassuring. Two offer no suggestion of bias at all. Of the 27 reports by female ethnographers (or by men with female field assistants), 23 report upright deliveries and only 4 report neutral ones. This is a higher proportion of upright reports than those by male ethnographers. If in fact the true proportion were equal, random sampling would produce so disparate a result in less than one sample in a thousand! Of the 59 ethnographers who display or claim some familiarity with the native language, 51 report upright deliveries while only 8 report neutral ones. This is a higher proportion of upright reports than that given by ethnographers who did not claim or display familiarity with the native language. If in fact the true proportion were equal, random sampling would produce so disparate a result in less than one sample in a thousand!

A higher proportion of reports are neutral in the last second stage test. Of the 49 ethnographers who stayed longer than a year in the field (or who were specially interested in childbirth and wrote a detailed and lengthy report on it), 38 reported upright deliveries, 11 reported neutral ones. This is a higher proportion of neutral reports than that given by ethnographers who did not stay a year or display a special interest in childbirth. However, the Chi square contingency test indicates that we would expect this extreme a result through mere sampling error from 28 per cent of random

samples from a universe in which there was no difference between the proportion of upright births reported by each class of ethnographer. All in all, then, we have no reason to believe that our conclusions are artifacts of second stage errors in which informants mislead ethnographers.

Third stage bias

Scientists rarely are concerned about deliberate frauds by other scientists. If such a fraud is detected, it of course means professional ruin to the perpetrator. Nevertheless, anthropology has witnessed its frauds—the Piltdown man hoax being the best known and most damaging. For a study of the sort we offer here, insurance against fraud is easily furnished by enabling the reader quickly and easily to check the work of the comparativist. All but three of the statements made here about childbirth positions are based on file slips under Rubric 844 of the Human Relations Area Files. Sets of these Files are available for checking at the following Universities: Chicago, Colorado, Cornell, Harvard, Hawaii, Indiana, Iowa, Michigan, North Carolina, Oklahoma, Paris (École pratique des hautes études), Pennsylvania, Princeton, Southern California, Southern Illinois, Utah, Washington, and Yale. The statements about conditions of research come from Rubric 844, Rubric 111, or Rubric 112 of the Files. Using Table I, a reader working with an efficient files curator can check half a dozen entries in half an hour. Data on 3 additional peoples not in the Files were volunteered by friends. Two of these 3 involved references to ethnographic literature on the Krangmalit Eskimo[3] and the Maori[1, 2]; these 2 peoples were added to the sample and data on them included in the statistical computations. The third came from Gerrold Tumes, M.D., of the University of California, Los Angeles, Medical Center. Tumes told us that while a tourist in Guatemala in 1956, he was called on to help deliver a Cakchiquel Indian woman with a breech presentation. Upon his arrival, he found the parturient normally clothed, in a squatting position with a Cakchiquel midwife working blind, her hands under the parturient's skirt. We did not add this anecdotal report to our sample or include it in the statistical computations. Concerning 4 peoples, the reports in the Files were ambiguous; the usual-normal position described could not be classified even tentatively as either upright or neutral; accordingly, these 4 peoples have been omitted from the study (Malaya, Shan Tai, Bontok, Marquesas).

A much more common source of third stage bias is the use of the forensic method—in which the comparativist collects favorable cases and ignores unfavorable ones. A sound method of sampling, coupled with faithful reporting of all cases found in the sample, is the best protection against deliberate or unconscious forensic bias. The Human Relations Area Files provides a worldwide sample chosen by anthropologists unconcerned with the problem of position of women in childbirth. Societies are chosen for the files in practice on one of two criteria. Either they are on a judgmental sample chosen by Professor George Murdock[15] and considered by him as a faithful reflection of the world's cultural patterns, or they are selected by an agency of the United States Government interested in collecting background information about certain regions of the world. While the Files are thus not in fact a random sample of the world's cultures, they are in a general way representative, in much the same way that the people who pass a downtown street corner are representative of the town's inhabitants. By strict statistical standards the Files must be presumed to contain significant and unknown selection biases. Yet there is no reason to suppose that these biases importantly affect the conclusion reached in this study. They certainly are independent of the authors of this report, who played no part in the selection of these societies. The report treats all the societies which had data on childbirth in the set of the Files at the University of Southern California in 1959.

A third possible source of comparativist's bias lies in the possibility that he may be a partial umpire, calling doubtful cases in fa-

vor of the home team. Actually, there is evidence that conscientious scientists are sometimes likely to produce the contrary bias, leaning over backward in favor of the visitors, so to speak.[6] Of the 104 reports on which we were able to reach a conclusion about the usual-normal position of women in childbirth, 96 were reports sufficiently explicit to leave no doubt. Reports using some form of the word "stand" or "squat" were classified as explicit reports of upright positions. Reports using a form of the word "kneel" or "crouch" were also classed as explicit reports of upright positions provided they also mentioned some kind of physical support for the parturient, either mechanical or human; but if no support was mentioned, they were classified as "upright suggested." Evidence of neutrality was deemed explicit if we were told that women lay down or that they squatted or kneeled, but partly supported themselves on their hands placed in front of them. In 15 societies, the position described was not clearly identifiable as upright or neutral, but we made inferences one way or the other from suggestions in the description: 12 of these we inferred to be upright, and 3 to be neutral. This is exactly the proportion of upright positions as that among the 89 explicit statements—a fact we did not know until after all these decisions were made.

Finally, in 6 of the 104 reports, the reporter described a single birth without saying whether or not the position taken by the woman was the general practice of the society to which she belonged. In 5 of these, the woman gave birth in an upright position, in the sixth, in a neutral position. Again, this is exactly the proportion of upright reports as that among reports made on general practice rather than on an individual birth.

The process as a whole

We have tested each step of the data collection process in turn. Now let us consider the process as a whole. Is there any evidence of a cumulative bias when the control factors are considered in combination? To test this hypothesis, an Observation Quality Index (OQI) is computed for each people in the sample. For this index one point is scored for each favorable observation condition. Where a second report on the same people corroborates the first report, we add the scores of each report, with an extra, bonus point for the fact of corroboration. Where a second report on the same people conflicts with the first report, we subtract the lower score from the higher and subtract also an extra penalty point for the fact of conflict.

The nonparametric Mann-Whitney "U" test was used to see if the neutral reports had a significantly higher average OQI than the upright reports. This test had negative results: although the average OQI of the neutral was slightly higher than that of the upright reports, a greater difference in either direction would be expected through chance alone in two random samples from the same population in 95 per cent of trials.

Summary

We have carefully examined for evidence on the position of women in childbirth 104 firsthand reports of anthropologists, government officials, missionaries, and other ethnographers from a sample of 75 non-European societies chosen by the Human Relations Area Files. In 62 of those, we believe, the women normally give birth in an upright position; in 14 (most of these in Asia) they normally give birth in a neutral position. We have systematically checked the whole data collection process for evidence of random error or of bias in the informant's mind, or in his communications with the ethnographer, or in the ethnographer's reports, or in our interpretation of these reports. Most of our statistical tests did not support the hypothesis of a bias in favor of upright position reports at all; and none of those that did was statistically significant. Hence, it seems to us clear beyond any reasonable doubt that in most non-European societies uninfluenced by modern Western medical practices women normally assume some kind of upright position in childbirth.

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Reviews | Abstracts

Edited by
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Book reviews

Atlas of Obstetric Technic. By J. Robert Willson. 304 pages, 55 plates. St. Louis, 1961, The C. V. Mosby Company. $14.50.

In this atlas consisting of 304 pages and more than 300 individual drawings the author has discussed and demonstrated the major techniques of present-day obstetrics. This atlas is by no means meant to supplant the standard texts but is devoted to the outlining of the manipulations and techniques which cannot be afforded a like space in a standard obstetric text because of the enormous amount of information on physiology, embryology, endocrinology, pathology, etc., contained therein. As a case in point I call the reader's attention to the chapter on breech delivery in which the author presents no less than 65 illustrations covering the intricacies of breech management with at least 9 plates on the management of extended and nuchal arms.

The book is divided into 14 chapters ranging from "Normal Labor and Delivery to "Cesarean Section," "Placenta Previa," and even "Craniotomy." In each of the chapters the special problem is concisely discussed as to the indications, contraindications, and details of management. Along with this discussion which is presented on the left-hand leaf, one may follow the details of management with the abundantly clear illustrations of Miss Daisey Stillwell which are arranged in a step-wise progression on the right-hand leaf.

The easy accessibility of the written information, the clarity of the illustrations, and the completeness of the coverage of obstetric techniques make this atlas a valuable tool for resident staffs, general practitioners, and specialists involved in the practice of obstetrics.

Lawrence Sonders

Die Intersexualitat. Edited by Claus Overzier. 560 pages, 193 illustrations, 38 tables. Stuttgart, 1961, Georg Thieme Verlag. $28.35.

This beautifully printed and bound volume represents a major contribution to the literature of intersexuality. It consists of a series of carefully prepared monographs by an outstanding international coterie of authorities on various phases of subjects. The book is designed to provide a comprehensive view of the contemporary status of well-established knowledge in the field of intersexuality, and in this it succeeds admirably. The editor, Professor Overzier, has imposed an impressive homogeneity of format on his distinguished panel of contributors. The quality of the illustrations is uniformly excellent and the thoroughness of the various bibliographies which end the individual chapters is uniformly commendable throughout the volume. The subject matter covered ranges widely over the field: representative sections include basic gonadal embryology, sex chromatin, nuclear sex in leukocytes, cytogenesis of human intersexuality, hormones in intersexuality, clinical methods of study of intersexual problems, nuclear sex in neoplasms, and specific clinical monographs on various types of intersexuality such as pseudohermaphroditism, gonadal dysgenesis, true Klinefelter syndrome, true hermaphroditism, and the relationship between intersexuality and transvestism. Of special value is the contribution of Barr on sex chromatin, and on the nuclear sex of the leukocytes. A brilliant chapter on the cytogenesis of human intersexuality by C. E. Ford of Harwell, England, is particularly impressive. Overzier and Hoffmann have provided

an exceptionally well-documented section on tumors with heterosexual activity. A short but extremely stimulating section on fundamentals of intersexuality has been contributed by Emil Witschi and J. M. Optiz of the State University of Iowa. This wealth of carefully presented material has been bound into an attractive volume with sturdy covers and legible print. Photographs, photomicrographs, and tables of all sorts are beautifully reproduced and excellently chosen.

Douglas M. Haynes

Current Therapy—1961. Edited by Howard F. Conn. 806 pages. Philadelphia, 1961, W. B. Saunders Company. $12.50.

The 60 pages in the section devoted to obstetrics and gynecology of this text sketchily cover close to two dozen significant topics in this field. Chapters on infant feeding and diseases of the breast have also found their way into this section. There are several high lights. The chapter on obstetric analgesia and anesthesia adequately summarizes the range of anesthetic agents and techniques, relating each to its effect on mother and infant. Experience suggesting that oxytocin alters reactivity of the motor end plate in the human, rendering is less susceptible to depolarizing blockade, is cited. Edward Mann, in the section on abortion, outlines his experience with habitual abortion and psychotherapy. The problem of varicosities in pregnancy is dealt with thoroughly in a chapter which concludes with a recommendation for concomitant postpartum tubal ligation and saphenous vein operation for multiparous patients with progressive, permanent varicose veins. The use of the newer progestational agents in the treatment of endometriosis, dysmenorrhea, and dysfunctional uterine bleeding is mentioned in the respective chapters.

The entire section on obstetrics and gynecology provides little new information for the specialist in this field.

Edward Wallach

Istopatologia Ginecologica e Gravidico-coriale. By G. B. Candiani and G. Remotti. 274 pages, 428 illustrations. Milan, Italy, 1960, Farmitalia.

The authors, both clinicians, have concentrated, in the 274 pages of this atlas, all the female genital pathological abnormalities, gynecologic as well as obstetric. The laconic text underlines an overwhelming number of remarkably good photomicrographs, mostly in black and white. The material from which the plates were obtained has been gathered entirely from the Department of Obstetrics and Gynecology of the University of Milano Medical School.

The editing is outstanding. The chapters relate to each particular segment of the female genital tract, with an introductory illustration of the normal histologic pictures. The breast is not included. Particular emphasis is laid upon the description of the neoplasms of cervix, endometrium, and ovary and on the pathology of the trophoblast.

It is worth noting that the description of the intraepithelial carcinoma of the cervix appears among the precancer lesions. A clear-cut histogenetic classification of the ovarian tumors is also made.

Carlo Valenti

Rypins' Medical Licensure Examinations—Topical Summaries and Questions. Edited by Walter L. Biering. Ninth edition, 805 pages, 26 tables. Philadelphia, 1960, J. B. Lippincott Company. $11.

The object of this book as stated in the preface is "not to teach the student anything new but to assist him in selecting and rearranging his material intelligently and practically."

Dr. Robert Nesbitt has produced a remarkable piece of work in his presentation of the scope of obstetrics and gynecology. This section is written in a precise, compact, and cogent manner where each sentence presents a valuable fact or reminder which in turn stimulates the opening of new areas of recall.

The rational arrangement of topics and the clarity of their presentation makes this an excellent aid in reviewing the fields of obstetrics and gynecology.

Lawrence Sonders

Dunham's Premature Infants. By William A. Silverman. 578 pages, illustrated. New York, 1961, Paul B. Hoeber, Inc. $15.

Dr. Ethel Dunham's *Premature Infants* is a classic treatise on the premature infant. The tremendous amount of new knowledge which has accumulated since the last edition published in 1955, has called for a complete revision of this authoritative book.

Dr. William Silverman, the author of this latest revision, is perhaps one of the best qualified persons to undertake this task. His extensive

clinical and investigative experience in this field enables him to present the material so that it is both comprehensive and practical. He covers every aspect of antenatal, perinatal, and postnatal care of the premature infant, yet one is never lost in a maze of details because the fundamentals are clearly applied to definite clinical situations. This book is of value to the clinical pediatrician, as well as to the research worker in pediatrics, or to anyone concerned with the care of the premature infant, such as the obstetrician or the pediatric surgeon.

The text is amply illustrated with numerous photographs and drawings. There is an excellent bibliography which follows each section. In addition to its intrinsic value as a source book, it is unusually well written and is easily understandable. *Ruth Achs*

Books received for review

At Your Best for Birth and Afterwards. By Eileen Montgomery. 59 pages, 20 figures. Baltimore, 1959, Williams & Wilkins Company. $1.75.

Blood and Other Body Fluids. Edited by Dorothy S. Dittmer. 540 pages, 166 tables. Washington, D. C., 1961, Federation of American Societies for Experimental Biology. $10.

Compendium of Pastoral Medicine. By Albert Niedermeyer. 492 pages. New York, 1961, Joseph F. Wagner, Inc. $7.95.

Control of Ovulation. Edited by Claude A. Villee. 251 pages, 14 tables. New York, 1961, Pergamon Press, Inc. $10.

The Couple Who Want a Baby. By Marie P. Warner. 244 pages. New York, 1961, Funk and Wagnalls. $3.95.

Diagnostic Cytology and Its Histopathologic Bases. By Leopold G. Koss and Grace R. Durfee. 380 pages, 776 figures. Philadelphia, 1961. J. B. Lippincott Company. $16.50.

Essential Hypertension—An International Symposium. Edited by K. D. Bock and P. T. Cottier. 392 pages, 81 figures. Berlin, 1960, Springer-Verlag.

Maimonides "On Sexual Intercourse." Edited by Morris Gorlin. 128 pages. Brooklyn, 1961, Rambash Publishing Co. $10.

Pregnancy and Diabetes Mellitus. By Lars Hagbard. 101 pages, 5 figures, 15 tables. Springfield, Ill., 1961, Charles C Thomas. $6.75.

The Premature Baby. By V. Mary Crosse. Fifth edition, 266 pages, 42 figures. Boston, 1961, Little, Brown & Company. $7.00.

Sterility—Office Management of the Infertile Couple. Edited by Edward T. Tyler. 425 pages, 23 tables, 21 figures. New York, 1961, McGraw-Hill Book Co., Inc. $12.50.

Recent Advances in Biological Psychiatry. By Joseph Wortis. Vol. III, 241 pages. New York, 1961, Grune & Stratton, Inc. $9.75.

Tumors of the Female Sex Organs. Part 3. Tumors of the Ovary and Fallopian Tube. By Arthur T. Hertig and Hazel Gore. 176 pages, 157 figures. Washington, D. C., 1961, National Academy of Sciences. $1.40.

You and Your Doctor. By William H. Potter. 288 pages. New York, 1961, Duell, Sloan & Pearce, Inc. $5.

Selected abstracts

New England Journal of Medicine
Vol. 264, No. 11, March 16, 1961.

Freedman, Daniel X., and Benton, Arnold J.: Persisting Effects of Reserpine in Man, p. 529.

Southern Medical Journal
Vol. 54, No. 3, March, 1961.

Hill, Hugh M., and Prystowsky, Harry: The Routine Use of the Papanicolaou Smear in Pregnant Women, p. 291.

Surgery, Gynecology and Obstetrics

Vol. 112, January, 1960.

*Franklin, R. E., and Brunson, J. G.: Rapid Identification of Malignant Cells in Vaginal Smears by Cytoplasmic Fluorescence, p. 3.

Franklin and Brunson: Rapid Identification of Malignant Cells in Vaginal Smears by Cytoplasmic Fluorescence, p. 3.

The authors report their experience on the staining of 864 smears obtained from 641 unselected gynecologic and obstetric patients at the University of Minnesota Hospitals by the acridine orange fluorescent dye method. The smears were taken by the physician or medical student who made the initial examination. A duplicate smear was made for independent examination by means of the conventional Papanicolaou method. The slides were fixed immediately in 95 per cent ethanol. The slides were then stained by a method outlined by the authors which is a modification of the procedure used by Bertalanffy. After the slides had been stained they were examined by means of a Spencer monocular microscope equipped with a special apparatus for fluorescence. A positive diagnosis of malignancy was made when the cytoplasm of several cells fluoresced an intense red-orange. All other slides were called negative. There was no intermediate category. There were 12 patients in which clinical, biopsy, and Papanicolaou evidence indicated malignancy. Only 7 of the 12 (58 per cent) had positive AO diagnoses on initial vaginal aspiration. Two of the 12 patients had recurrent postirradiated squamous cell carcinoma of the cervix, neither of which were identified by AO fluorescence. Thus 7 of 10 (70 per cent) primary malignant neoplasms were identified properly by AO fluorescence of cytoplasm. There were 629 patients in whom no malignant neoplasm was present. In 15 of these the smears were considered inadequate. Of the remaining 614 patients 603 (98 per cent) were eliminated correct. Of the 11 AO false-positives, 6 were from cases of postirradiated squamous cell carcinoma of the cervix, one was from the pregnant patient, one from a patient with a healed cervical laceration and three were from asymptomatic patients. Altogether smears from 18 patients were called AO positive. Seven patients (44 per cent) actually had a malignant neoplasm. The value of this method of cancer detection is primarily in those cases in which there is a rapidly proliferating type of malignant process. This process is usually present in the rapidly growing early cases. Therefore, this procedure is of value in the screening of such cases. However, it has many shortcomings in determining the presence of recurrence of malignant neoplasms in previously irradiated patients.

J. Edward Hall

*These articles have been abstracted.

Zentralblatt für Gynäkologie

Vol. 82, No. 31, July 30, 1960.

Mischel, W.: Choline Content of the Amnion, Umbilical Cord, and Amniotic Fluid at Term, p. 1169.

Niesert, W.: Chorio-adenoma Destruens and Spontaneous Rupture of the Uterus—Case Report, p. 1178.

Szinnyai, M., and Hunka, R.: Follow-up for Pre-diabetes on Mothers of Babies With Excessive Birth Weight, p. 1184.

Lakatos, I.: Fibrinogen Therapy for Coagulation Disturbance in Pregnancy—Case Report, p. 1189.

*Margitay-Becht, M.: Colposcopy in Pregnant and in Sterile Women, p. 1193.

Alessandrescu, A., and Dumitrescu, A.: Is Spinal Anesthesia Advantageous for Cesarean Section? p. 1198.

Bielfeld, K.: The Use of a New Phenothiazine Derivative in Obstetrics, Especially in Labor, p. 1206.

Margitay-Becht: Colposcopy in Pregnant and in Sterile Women, p. 1193.

Among 7,600 sterility and 10,000 obstetrical patients ranging in age from 20 to 35, colposcopy was done for erosion on 947 and 2,053 women, respectively. Carcinoma was found in 3 sterile (0.3 per cent) and 2 pregnant (0.1 per cent) women (percentages are based on colposcoped patients). All 5 of the "positive" women were between 30 and 35. Other epithelial pathology was found in 26 per cent of the sterility patients and 12.6 per cent of the pregnant women who were colposcoped.

Walter F. Tauber

No. 35, Aug. 27, 1960.

*Luft, H.: Choice of Method of Delivery in Cardiac Patients, p. 1329.

Kovacs, L., and Makay, L.: The Question of Etiology of Malformations, p. 1335.

Sievert, C., and Schönermark, J.: Contribution on the Clinical Picture in Congenital Anophthalmia, p. 1342.

Skamnakis, S., and Schmidt, K.: Unusual Genital Malformations and Pregnancy—Case Report, p. 1344.

Rysanek, M.: Pseudocyesis Following Total Hysterectomy—Case Report, p. 1347.

Haller, J.: Dermoid Cyst Obstructing Delivery in a 17-year-old Primigravida, p. 1353.

Spielmann, W., and Gottlob, R.: Therapy of Severe Uterine Perforation Following Criminal Abortion, p. 1355.

Luft: Choice of Method of Delivery in Cardiac Patients, p. 1329.

Among 17,934 patients delivered between 1955 and 1959, there was an incidence of 1.7 per cent of heart disease (305), with 0.23 per cent (41) Classes II to IV. Only one mother, who was admitted in failure during labor, died. Prenatal care followed the usual criteria for restricted activity, digitalis administration, and hospitalization used also in the United States. In labor, particular attention was given to spasmolytics and analgesia. Autonomic drugs were continued into the puerperium.

Method of delivery is analyzed for 19 cardiac women (out of 7,398 deliveries) in 1958 and 1959. There were 4 cesarean sections (21.1 per cent) for heart disease alone, 5 (26.3 per cent) cesarean sections with additional obstetrical indication, 3 (15.8 per cent) vacuum extractions, 1 (5.3 per cent) assisted breech delivery, and 6 (31.6 per cent) spontaneous deliveries. Apparently there were no forceps deliveries, though in the discussion the author advocates shortening the second stage if vaginal delivery is elected. The author states that under modern methods of anesthesia there is less strain on the heart in cesarean section than in labor and vaginal delivery. *Walter F. Tauber*

Items

American Board of Obstetrics and Gynecology

The next scheduled examination (Part I), written, will be held in various cities of the United States, Canada, and military centers outside the Continental United States, on Friday, Jan. 5, 1962.

Current Bulletins may be obtained by writing to Robert L. Faulkner, M.D., Executive Secretary and Treasurer, 2105 Adelbert Road, Cleveland 6, Ohio.

Diplomates of this Board are urged to notify the Office of the Executive Secretary and Treasurer of a change in address.

Society for Scientific Study of Sex

The Fourth Annual Meeting of The Society for the Scientific Study of Sex will be held at 9:30 A.M., Nov. 4, 1961, in the Barbizon-Plaza Hotel, 106 Central Park, South, New York, New York.

The topic for the morning session is "Sex and Aging" and of the afternoon session "Sex Factors in Schizophrenia."

For further information apply to Dr. Hugo G. Beigel, Secretary, 138 East 94th Street, New York 28, New York.

University of Hue in Vietnam

The American Friends of Vietnam is seeking copies of the JOURNAL for years prior to 1960, to be sent to the newly opened medical school of the University of Hue in Vietnam. Copies that can be contributed should be sent to the American Friends of Vietnam, 4 West 40th Street, New York 18, New York.

Symposium on Basic Problems in Neoplastic Disease

Columbia University College of Physicians and Surgeons is sponsoring a 3 day symposium titled "Basic Problems in Neoplastic Disease" to be held on March 12, 13, and 14, 1962. This symposium will commemorate the fiftieth anniversary of the Institute of Cancer Research at Columbia University and the tenth anniversary of its affiliated clinical facility, The Francis Delafield Hospital.

An outstanding group of scientists from the United States and abroad will participate in sessions titled as follows: Nucleic Acid Structure and Synthesis; Viral and Genetic Studies; Protein Synthesis; Antibody Structure and Function. In addition, sessions devoted to clinical aspects of the biochemistry, pathology-physiology, morphology, and therapy of cancer will be held.

The symposium is open without fee to all interested workers in this field. For details concerning the meeting, including application to attend sessions, write to the Institute for Cancer Research, Columbia University College of Physicians and Surgeons, 630 West 168th Street, New York 32, New York.

Conference on "The Cervix"

The New York Academy of Sciences will sponsor a conference on "The Cervix," Dec. 7, 8, and 9, 1961, at The Barbizon-Plaza Hotel, New York City.

Conference co-chairmen are Warren R. Lang, Jefferson Medical College, Philadelphia, Pennsylvania, and Alfred B. Kupferberg, Ortho Research Foundation, Raritan, New Jersey.